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Target Audience

This journal supplement is intended for dermatologists, family practitioners, internists, registered nurses, nurse practitioners, physician assistants, and other clinicians who treat patients and practice medical and/or aesthetic dermatology.

Educational Needs

Seborrheic keratoses (SKs) represent the most common benign tumor in humans and are among the most frequent reasons for visiting a dermatologist. SKs can mimic or mask cutaneous malignancy. Clinicians should be able to diagnose SKs efficiently and accurately to avoid missing melanoma or other cancers. Medical intervention is not required unless the diagnosis is uncertain or the SKs are symptomatic (eg, bleeding, irritation, or itching). Patients with benign lesions often express interest in treatment due to the emotional and social impact of SKs. Current destructive options can be associated with pain, scarring, and pigmentary abnormalities. The first topical therapy approved for use on SKs—hydrogen peroxide topical solution, 40% (HP40)—received US Food and Drug Administration approval about 1 year ago. Clinicians need to be aware of and sympathetic to patient concerns about SKs and treatments. They also benefit from being informed about the latest therapeutic options for removing SKs.

The ASK Initiative™

Advances in Seborrheic Keratosis

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Seborrheic keratosis (SK) has been called the "Rodney Dangerfield of skin lesions"—it earns little respect (as a clinical concern) because of its benignity, commonality, usual ease of diagnosis, and simplicity of treatment.[1] But these humble lesions are deceiving: They can mimic or camouflage cutaneous malignancy, signal internal malignancy, and cause substantial distress for patients.[2-5] Understanding why they remain benign despite the presence of mutations also found in cancer cells may lead to new therapies for cancer—and for SKs.[1,6]

Recently, the US Food and Drug Administration (FDA) approved the first topical therapy—hydrogen peroxide topical solution, 40% (HP40)—for use on raised SKs, offering clinicians an effective and nondestructive option for removing these lesions. Unlike some topical dermatology products, HP40 is distributed only through dermatology practices and must be applied by a clinician.[7] This article offers an update about the management of SKs and the use of this new therapy.

SKs—commonly called age spots—represent the most common benign tumor in humans and are among the most frequent reasons for a visit to a dermatologist.[1,8] The lesions of SK typically appear as round or oval, sharply demarcated verrucous plaques with a waxy, stuck-on appearance and with variable thickness and color. As their vernacular name implies, they become more prevalent with advancing age. One author estimated that 80% to 100% of individuals older than 50 years will develop at least one SK.[9] Although characteristically observed in middle-aged to older adults, they also occur in teens and young adults.[10] SKs rarely travel alone; most individuals with SKs have more than one such lesion. In one study (N=406), the average number of nonsymptomatic SKs per patient was 26.[11]

SKs result from the accumulation of normal keratinocytes between the basal layer and the keratinizing surface.[12] They can develop virtually anywhere except for the palms, soles, and mucous membranes,[9] but are most commonly observed on the trunk and face.[6,13] The tendency to develop SKs can run in families; some genetic links have been identified.[14,15]

SKs are associated with an extremely low risk of malignancy. They can expand and thicken with time,[6] however, and may be mistaken for melanoma and other skin cancers.[4] Patients may regard the lesions as unsightly, annoying, or irritating, especially if the lesions are visible or rub against clothing.

Pathophysiology

Despite the ubiquity of SKs, little is known about their pathophysiology. Researchers recently reported that the signaling kinase Akt is important to their survival. Inhibiting this enzyme with ATP-competitive Akt inhibitors such as A443654 induced SK apoptosis.[6] ATP-type Akt inhibitors tested in this study did not affect the survival of primary human keratinocytes or of squamous cell carcinoma (SCC) cell lines. This finding is noteworthy because some genomic alterations in SK lesions are similar to, or overlap with, those of SCC cells.[16] Most (80%) SKs had at least one mutation in an oncogene; nearly half (45%) of SKs had oncogenetic mutations in two genes, in one study.[17] Learning why SKs remain benign despite the presence of such genomic alterations in major signaling pathways may suggest new treatments for cancers.[6]

Diagnosis

SKs typically are diagnosed clinically, with biopsy performed for ambiguous lesions. The appearance of SKs varies widely, presenting as rough and keratotic, smooth and waxy, or flat and macular.[13] Pigmentation can be absent (pink or white), but they usually appear gray, dark brown, or black. Size generally ranges from 0.5 to 1.5 cm. Dermatosis papulosa nigra—dark brown or black papules—are

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Differentiate between benign seborrheic keratosis (SK) and other common skin lesions
- Recognize the potential emotional and social impact of SK lesions on patients
- Design a therapeutic approach for individual patients with SK lesions that maximizes outcomes while minimizing adverse events.

Disclosure Declarations

Individuals in a position to control the content of this educational activity are required to disclose: 1) the existence of any relevant financial relationship with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients with the exemption of non-profit or government organizations and non-health-care-related companies, within the past 12-months; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Joseph F. Fowler Jr, MD, Speakers Bureau: Smart Practice, Regeneron; Grant/Contracted Research Support: Aclaris Therapeutics, Galderma Laboratories, Pfizer, Novartis, Lilly, Accuitis, Dermira, Ralexar, and Regeneron. He will discuss the investigational/unlabeled uses of A-101 40% solution; 5% potassium dobesilate cream; aqueous trichloroacetic acid (TCA) and formic acid combination; tazarotene 0.1% cream; A-443654; GSK690693.

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smaller than other SKs and are found more commonly in patients with darker skin types.[9,15] Stucco keratoses typically present as multiple, flesh-colored, dry, well-circumscribed, scaly, flat-topped papules commonly seen on the lower legs and dorsum of the hands.[9]

Dermoscopy can aid in the assessment of ambiguous SKs and reduce the need for patients to undergo the physical and emotional trauma of a biopsy. An algorithm for dermoscopic diagnosis of SKs has demonstrated a sensitivity of 95.7% and a specificity of 78.3% (see "A 2-Step Algorithm for Dermoscopic Diagnosis of SKs").[18]

A 2-Step Algorithm for Dermoscopic Diagnosis of SKs[18]

- Step 1: Multiple milia-like cysts; comedo-like openings; fissures/ridges (brain-like appearance); light-brown fingerprint-like structures; and the lack of blue-gray or blue-white color
- Step 2: Sharp demarcation, mica-like structure, and yellowish color.

Sensitivity and specificity for diagnosis of SK: 95.7% and 78.3%, respectively

Source: Lin et al.[18]

Distinguishing SKs from cancers

Even under dermoscopy, some SKs can resemble other lesions, including melanoma, melanocytic nevus, basal cell carcinoma (BCC), or SCC (**Table 1**).[4] Characteristics demonstrated to distinguish dermoscopically SK-like melanomas from SKs include the blue-black sign, the blue-white veil, pseudopods or streaks, and a pigment network.[2]

Cancerous lesions can arise within or adjacent to SKs, complicating diagnosis and obscuring the malignancy amid the surrounding SKs. SCCs have reportedly arisen within SKs; these so-called SCC-SKs have histological features of both lesion types. Risk factors for these lesions include a history of skin cancers and immunosuppression, especially when immunosuppression is associated with transplantation.[12]

A biopsy should be performed when the diagnosis is unclear to rule out carcinoma.

When SKs signal internal malignancy

A sudden increase in the size and number of SKs can herald the presence of internal malignancy. This finding, known as the sign of Leser-Trélat, is most often associated with gastric adenocarcinoma but also is observed in conjunction with cancers of the bladder, kidney, prostate, lung, and/or ovaries, as well as lymphoproliferative abnormalities and melanoma.[3,5] Symptoms of pruritus and acanthosis nigricans may be associated with the sign of Leser-Trélat.[3]

These so-called SK eruptions also occur in the absence of malignancy, when they are known as the pseudo-sign of Leser-Trélat.[3] Treatment with adalimumab has been associated with pseudo-sign of Leser-Trélat.[20] All patients who appear to have the sign or pseudo-sign of Leser-Trélat should be screened for malignancy.[5]

Treatment

Medical reasons to remove SKs—other than diagnostic ambiguity—include irritation, ulceration, or bleeding. Insurance may cover their destruction under these circumstances. Patients often seek removal of SKs because they find the lesions annoying or unsightly, or out of concern that the lesions may develop into something more serious.[11] Treatment of non-symptomatic lesions with an unambiguous diagnosis is generally considered to be a cosmetic procedure for which the patient must pay out of pocket.

Destructive interventions

Cryosurgery is the first choice for treating most SKs, due to its rapidity, availability, and ease of use. Flat SKs can be reduced or cleared in a single 5- to 10-second freeze/thaw cycle, whereas thicker lesions may require longer freeze times or multiple cycles.[21] Other options include curettage and electrocautery

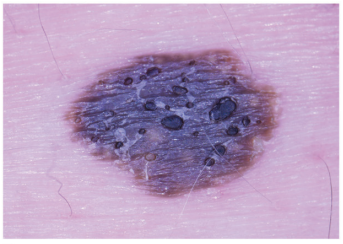
Table 1. Dermoscopic Findings: SK or Malignancy?

Dermoscopic Findings	In SKs	In Non-SK Lesions
Fissures and ridges	Thick, curved, occasionally branched lines whose colors vary from hypopigmented to brown, black, and blue	Can mimic the pigment network of melanocytic lesions, in which lines are typically thinner. Use ink test to aid in diagnosis[19] See online sidebar, Practice Pearls for SK Diagnosis and Treatment.
Hairpin vessels	Two parallel linear vessels forming a half-looped or hairpin-like structure, often surrounded by a white halo	Also observed in melanoma, SCC, and BCC; presence supports but does not make diagnosis of SK
Milia-like cysts	Many (>3) small (<1/3 mm) milia-like cysts throughout the lesion ("stars in the sky")	Few milia-like cysts suggest melanocyte nevus, melanoma, or BCC
Polymorphous vascular pattern, ulceration, or crust	Observed in irritated or traumatized SKs	Suggests SCC/keratoacanthoma if accompanied by pronounced abnormal keratinization, white circles, keratin, and blood spots
Globule-like structures	Observed in clonal type SK and regressing SK	May resemble blue-gray globules and blue-gray ovoid nests of BCC

BCC, basal cell carcinoma; SCC, squamous cell carcinoma; SK, seborrheic keratosis.

Source: Minagawa.[4]

Melanoma or SKs?



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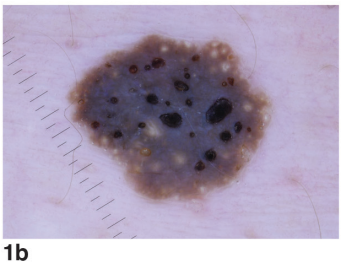

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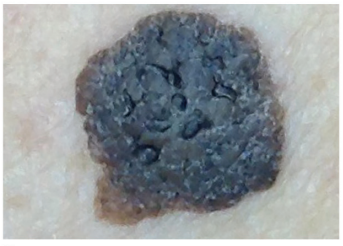

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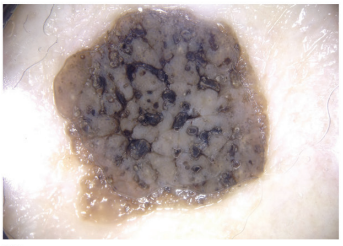

2b

Clinical images (Figures 1a and 2a) display features of melanoma (asymmetry, irregular borders, color variegation, large diameter). Dermoscopic images of the same lesions (Figures 1b and 2b) reveal features diagnostic for SKs (eg, sharp demarcation, milia cysts, comedo-like openings). Both lesions are SKs.
Source: Ashfaq A. Marghoob, MD.

or, for certain lesions, laser therapy. A petrolatum ointment can be applied to the treatment areas after either intervention, and wounds can be covered by a dressing after curettage and electrocautery. Patients should be advised not to apply topical antibiotics to the wounds because of the risk of contact dermatitis without improved healing.[22]

All destructive procedures are associated with erythema, postinflammatory hypopigmentation, and postinflammatory hyperpigmentation. Postinflammatory hyperpigmentation occurs more commonly in patients with darker skin types (Fitzpatrick skin types IV-VI) and results from an increased deposition of melanin in the skin after cutaneous inflammation or injury. This outcome can be distressing to patients. Hyperpigmentation may require several months or years to resolve, even with treatment.[23] Hypopigmentation is less well understood, but also occurs more often in individuals with darker skin types.[13] Occurrence of pigmentary changes depends somewhat on the expertise of the person performing the procedure, in addition to the patient's skin type. All patients should be informed about the risk of these adverse events.

A study (N=25) comparing outcome of, and patient preference for, the method of removing SKs from the trunk or proximal extremities found that at least 60% of patients preferred cryosurgery over curettage, at 6 weeks and more than 12 months posttreatment. On a scale of 1 (lesion unchanged) to 10 (normal-appearing skin), patients rated the cosmetic outcome positively and similarly with each intervention—8.58 and 9.33 with cryosurgery and 8.28 and 9.39 for curettage at 6 weeks and more than 12 months postintervention, respectively.[24]

Patients noted more pain with treatment during cryosurgery; individuals undergoing curettage received local anesthesia with 1% lidocaine. Some patients indicated a preference for cryosurgery because of the reduced need for postoperative wound care. Physicians indicated that curettage was associated with more erythema at 6 weeks and a greater tendency for hypopigmented scar formation after 12 months (rates not reported). All patients had relatively light skin (Fitzpatrick skin types I-III).[24]

Authors have reported successful treatment of SKs with ablative (eg, erbium:YAG)[25] and nonablative (long-pulsed 755-nm alexandrite)[26] lasers. In one study of 42 patients with SKs of 0.5 to 3 cm, one lesion on each patient was treated with an erbium:YAG laser and one with cryotherapy. All laser-treated lesions had healed at 4 weeks postprocedure, compared with 68% after cryotherapy ($P<0.01$).[25]

Nonablative lasers are believed to treat SK lesions by targeting melanin

Managing SKs: Case Vignettes

Case 1. A Woman With Multiple Lesions on the Face and Neck

Danielle Y., a 57-year-old African American woman, presented to an aesthetic dermatologist with five small, darkly pigmented papule-like lesions on her face and neck. She denied experiencing pain or itching in those areas and recalled no trauma, infection, or other circumstance that would account for them. Her primary care provider (PCP) diagnosed the lesions as dermatosis papulosa nigra, then referred her to the aesthetic dermatologist to discuss potential options for treatment. The PCP informed her that the lesions are benign with no malignant potential.

Danielle works as a buyer for a major retail clothing company. She said that her job includes frequent in-person customer interactions and presentations. Her mother and aunt have many more lesions similar to hers, and she is concerned about the negative effect on her professional appearance if additional lesions develop. Having had other aesthetic dermatologic interventions, she understands that she will have to pay for lesion removal out of her own pocket.

The aesthetic dermatologist explains the options of cryosurgery, curettage and electrocautery, laser therapy, and topical therapy. He notes the risk of postinflammatory pigmentary disorders in patients with skin of color after any of these interventions. He explains that the topical therapy is associated with mostly mild levels of hyperpigmentation and hypopigmentation in, respectively, 8% and 3% of patients roughly 3 months after the first treatment, in a population of mostly light-skinned individuals.[1]

Danielle is very concerned about the possibility of destructive interventions worsening her appearance. She suggests trying the topical on one or two lesions to assess the response. The dermatologist agrees to this plan.

Case 2. A Man With a Pigmented Lesion on the Neck

Alan W., a 79-year-old white man, presented to his dermatologist for a quarterly skin examination. As a light-skinned individual (Fitzpatrick type II) with a history of severe sunburn while on surface ship duty in the Navy, he is at risk for dermatologic malignancies. He has had multiple precancerous lesions removed in the last 5 years or so.

The dermatologist noticed that a thick (~4 mm) pigmented lesion on the back of the neck near the hairline had enlarged and appears to have darkened since the last examination. The lesion was first noted many years ago and had remained unchanged, until today. The dermatologist had previously diagnosed it as a seborrheic keratosis (SK), for which Alan declined treatment. Dermoscopic examination does not clarify the diagnosis. Given the patient's history, the dermatologist biopsies the lesion.

The biopsy indicates that the lesion is an SK. The patient has had cryosurgery in the past and found the procedure very painful. He expresses a desire to avoid it. The dermatologist recommends electrocautery and curretage, for which the patient will receive anesthesia with 1% lidocaine and after which some wound care will be required. The patient agrees.

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Additional images and content are available online at ***https://tinyurl.com/SebKeratosis*** *"Practice Pearls for SK Diagnosis and Treatment," "Applying Hydrogen Peroxide Topical Solution, 40% (HP40)," "How Patients Feel About Their Seborrheic Keratoses," and "Managing SKs in Medical and Aesthetic Dermatology Practices."*

pigments, suggesting that they would be ineffective in lesions with little pigmentation. However, a study using the long-pulsed 755-nm alexandrite laser on 216 SKs in 13 patients with Fitzpatrick skin types III or IV reported a mean objective improvement score of 3.4 on a scale of 4, with 4 as the highest rating. Blinded dermatologists rated improvement based on photos taken before and 2 months after final treatment. Neither lesion color nor characteristic (macular, papular, or verrucous) affected improvement score. Most lesions became crusted after a few days and peeled off within 7 days. Erythema generally resolved within 2 hours, persisting for 2 months in two patients. Hypopigmentation developed in two patients, hyperpigmentation (that gradually improved) developed in one patient, and some scarring occurred in one patient.[26]

Topical therapy

Two identically designed phase 3 trials of HP40 were conducted in patients with lesions that were no more than 2 mm thick and 5 to 15 mm in length and width.[27] Patients (N=937) with four SKs each were randomized 1:1 to HP40 or vehicle. Efficacy was assessed using the Physician's Lesion Assessment (PLA) scale (0, clear; 1, nearly clear; 2, ≤1 mm thick; and 3, >1 mm thick). SKs with a score of more than 0 were re-treated 3 weeks later. Significantly higher proportions of patients receiving HP40 attained the primary endpoint, which required all four lesions to be completely clear at day 106 (**Table 2**). Other efficacy measures also favored HP40. One-quarter of lesions treated with HP40 were rated nearly clear (PLA, 1) after the first treatment.[27]

Erythema, edema, stinging, pruritus, and vesicle formation were reported within 10 minutes of the first HP40 treatment for 91%, 75%, 71%, 18%, and 12% of lesions, respectively. Most reactions were mild or moderate. Reactions observed 1 week after the initial HP40 treatment included scaling (49% of lesions), crusting (45%), hyperpigmentation (5%), erosions (3%), hypopigmentation (2%), and scarring (0.2%).[27]

Local skin reactions generally had resolved by day 106. The most common local skin reactions at day 106 by percentage of lesions were erythema (10%), scaling (8%), hyperpigmentation (8%), crusting (5%), and hypopigmentation (3%); patients rated more than 99% of reactions as mild.[27]

Most (98%) patients in these studies were white; about 10% were Fitzpatrick skin types IV-VI.[27] An ex vivo study of skin derived from Fitzpatrick skin type V suggested that, compared with cryosurgery, HP40 is associated with less cytotoxicity and greater melanocyte viability.[28] A phase 2 study of patients with dermatosis papulosa nigra is in progress (ClinicalTrials.gov, NCT03224598). A phase 4 study of patient satisfaction with HP40 treatment applied to lesions on the face, neck, and décolletage is also underway (ClinicalTrials.gov, NCT03487588). The online sidebar "Applying Hydrogen Peroxide Topical Solution, 40% (HP40)" describes how to administer the therapy.

Table 2. Efficacy of HP40 in 2 Identical Phase 3 Trials

Endpoint	HP40		Vehicle		*P value*
	Study 1	Study 2	Study 1	Study 2	
Percent of patients, PLA score of clear, all 4 lesions, day 106*	4%	8%	0%	0%	0.01
Percent of patients, PLA score of clear, 3 of 4 lesions, day 106	13%	23%	0%	0%	0.0001
Mean per-patient percentage of SKs rated clear, day 106†	25%	34%	2%	1%	NR
Mean per-patient percentage of SKs rated clear or almost clear, day 106†	47%	54%	10%	5%	NR

PLA, Physician's Lesion Assessment scale (0, clear; 1, nearly clear; 2, ≤1 mm thick; and 3, >1 mm thick).
*Primary endpoint; †exploratory analyses; NR, not reported.
Source: Baumann et al.[27]

The patient's view of SKs

In one interview-based study, 55% of 406 adult patients with nonsymptomatic SKs said they had initiated conversations with their dermatologists about their lesions.[11] Patient self-reported reasons for removing nonsymptomatic SKs in this study included concern the lesions may be something serious (57%), as well as not liking the appearance of the lesion (53%) or how the lesions feel when touched (44%). Slightly less than half of patients (45%) cited equal concerns about health and appearance as reasons for seeking treatment for SKs. A majority (61%) said that they tried to hide their lesions with, for example, clothing, hairstyles, or makeup.[11] For more information, see the online sidebar, "How Patients Feel About Their Seborrheic Keratoses."

Summary

SKs are a common, benign lesion that are among the most frequent reasons for a visit to the dermatologist.[8] Their simplicity may obscure the fact that they can mimic malignancy, hide malignancy, and signal internal carcinoma. A new FDA-approved topical therapy for raised SKs offers an option for individuals who prefer to avoid destructive interventions. Ongoing research into why these lesions remain benign may reveal new therapies for malignancies as well as for SKs.

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