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Target Audience

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

Educational Needs

Seborrheic keratosis (SK) is a common and benign skin lesion that affects more than 80 million Americans. Medical intervention is not required unless the diagnosis is uncertain and a biopsy is indicated, or unless the SKs are symptomatic (pruritus, irritation, or bleeding). Still, many patients seek medical advice because of cosmetic issues or concerns about the possibly malignant nature of the lesions. Current treatment modalities involve tissue destruction, which poses a risk for scarring, hyper- or hypopigmentation, or other unwanted sequelae. Future treatments may offer a topical approach that reduces the risk of unacceptable outcomes. Clinicians should be able to diagnose SK accurately and efficiently, and should be aware of current and emerging treatment strategies.

Learning Objectives

By reading and studying this supplement, participants should be better able to:

- Differentiate seborrheic keratosis (SK) from other skin lesions
- Describe current and emerging treatment options for SK
- Match patients with the most appropriate interventions for effective removal of SKs, including those in cosmetically sensitive areas, such as the face and neck

Update on Seborrheic Keratosis: Optimizing Patient Outcomes

FACULTY



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Seborrheic keratosis (SK) is a common benign lesion, usually round or oval, ranging from light tan to dark brown. SK lesions affect 1 out of 5 Americans, particularly those older than 50 years. Clinicians must accurately diagnose SK lesions before removing them. SK lesions are benign and can be removed for cosmetic reasons if the patient desires; treatment may be indicated—and reimbursable—if the lesion is irritated. In the case of suspicious lesions, clinicians should perform a shave biopsy to ensure that they are not premalignant or malignant tumors. Choice of treatment is based on the number of lesions, location on the body, skin pigmentation, thickness of the lesion, and overall esthetic considerations. Cryosurgery is the method preferred by most physicians for removing these lesions; other methods include curettage, electrosurgery, lasers, and a combination of modalities. Emerging topical therapies may provide effective lesion removal without the adverse effects seen with cryotherapy, lasers, or other standard modalities.

Some 83 million Americans—approximately 20% to 25% of the population—are affected by SK.^{1,2} These benign lesions are usually seen in people older than 50 years.² SK lesions are equally distributed among men and women, although a recent

survey of patients with SK found a slightly higher rate among men.² Furthermore, SK is thought to be more prevalent in Caucasians, but a variant form known as dermatosis papulosa nigra can affect people with Fitzpatrick skin type VI (Table 1).^{3,4}

These SK lesions can develop anywhere except the palms and soles. They appear most frequently on the trunk and somewhat less often on the arms, face, and neck.^{2,3} The lesions tend to be round or oval and are from 0.5 to 1.5 cm in diameter; they can range in color from light tan to dark brown. The term *seborrheic* refers to the lesions' rough or waxy appearance (Figure).^{2,3,5} The presentation of SK lesions is highly variable, which has led to the use of several synonyms to identify the condition, including basal cell acanthoma, basal cell papilloma, benign acanthokeratoma, verruca seborrhoica (seborrheic wart), and verruca senilis (senile wart).³

A study of more than 4000 cases characterized the subtypes of SK lesions. The 5 patterns found most frequently were⁵:

- Multicomponent (19.9%) lesions, which involve a combination of ≥3 distinct structures
- Reticular (14.9%) lesions which have a deep brown pigment with thin brown lines at the border, a pattern found in solar lentigo or Clark nevus

Table 1. Fitzpatrick Skin Phototypes⁴

Skin Type	Typical Features	Tanning Ability
I	Pale white skin, Blue/green eyes, Blond/red hair	Always burns, Does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

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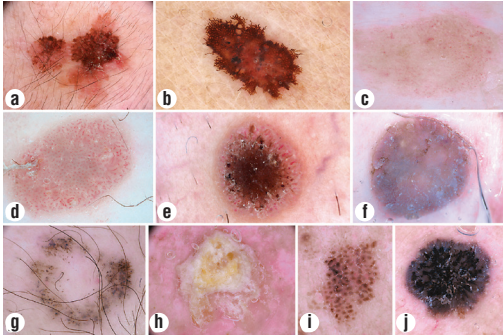
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Figure. Types of Seborrheic Keratosis Lesions⁵



a. Multicomponent (≥ 3 distinctive structures); b. Reticular; c. Bowenoid; d. Hairpin; e. Keratoacanthoma-like; f. Blue-like; g. Lichenoid; h. Hyperkeratotic; i. Clonal; j. Spitzoid.

Source: Squillace L, et al.⁵ Copyright © 2016, Karger Publishers, Basel, Switzerland. Used by permission.⁵

For additional photos of SK lesions, visit the online version of this supplement at <https://tinyurl.com/sebksuppl17>

- Bowenoid (13.0%) lesions, which have glomerular or dotted vessels, or combinations of both
- Hairpin (11.8%) vessels, which cover most of the SK lesions and have hematic crusts
- Keratoacanthoma-like (9.9%) lesions, which have keratotic structures with blood crusts, pink appearance, and linear vasculature

There is no definitive cause for SK; however, the lesions frequently appear on areas of the body that are exposed to the sun.¹ Because lesions are also found in intertriginous areas, such as the axillae or abdominal folds, sunlight cannot be implicated in every instance.¹ Other potential causes include viruses, such as human papillomavirus, and genetic mutations.^{1,3}

Recent investigations have identified genetic processes involved in the formation of SK lesions.^{3,6} Fibroblast growth factor receptor 3 (*FGFR3*) plays a key role in SK lesion development.³ Mutations of the *FGFR3* gene have been found in up to 85% of SK cases.³ Germline mutations in this gene have been associated with craniosynostoses and skeletal dysplasia.³

Another gene associated with SK is the *PIK3CA* gene, which has oncogenic properties and is found in malignant tumors of the colon, breast, and bladder.³ One study found that 45% of SKs have more than 1 gene mutation in oncogenes such as *FGFR3*, *PIK3CA*, *KRAS*, or

EGFR.⁶ Furthermore, SK lesions are thought to occur in the receptor tyrosine kinase/phosphatidylinositol 3-kinase/Akt signaling cascade, which is seen in squamous cell carcinoma.⁶ Preliminary evidence suggests that suppressing Akt signaling may induce cell death of SK and thus eradicate the lesions.⁶

Patients often present to their clinicians because they are concerned about potential malignancy or the unsightliness of the condition.² Many dermatologists do not routinely recommend treatment for benign SK lesions unless the lesions have become irritated, leading to pruritus and/or bleeding.

The challenge for clinicians is that benign tumors may masquerade as more serious skin lesions, such as melanoma in situ or squamous cell carcinoma. However, SK lesions are usually distinguished by the horned cysts that can be seen on dermatoscope examination (Table 2).^{1,3}

When examining a pigmented lesion, clinicians should use what is known as the 7-point checklist.⁷ This list, originally developed for British primary care clinicians, assigns a score to assess the severity of lesions. The 3 most critical risks for malignancy—change in lesion size, irregular border, and irregular pigmentation—are given a weighted score of 2 points. The minor factors, worth 1 point each, are inflammation, pruritus, diameter of > 7 mm, and crusting of the lesion. A score of ≥ 3 indicates a lesion that should be referred to a dermatologist.⁷ In primary care practices, the checklist's sensitivity was 73.3%, and its specificity was 57.1%.

Because SK is among the most frequently diagnosed lesions in dermatology, clinicians can become complacent about its diagnosis. Such complacency should be avoided; in a retrospective study of 577 SK lesions, 6.4% were eventually found to be malignant tumors.⁸ A timely diagnosis that differentiates SK and melanoma is essential for long-term survival. Melanomas that are < 1 mm in depth have a 95% 5-year survival rate; however, patients whose melanoma is > 4 mm thick have only a 45% 5-year survival rate.⁹

Experienced dermatologists can easily distinguish SK lesions from more serious and potentially malignant lesions. At a minimum, visual examination under proper lighting will aid in the diagnosis; simply touching the lesion will distinguish between a flat and a rough surface. In many cases, dermatoscope examination can

Table 2. Differential Diagnoses of Seborrheic Keratosis^{1,3}

Permanent or Malignant Lesions	Benign Lesions
• Actinic keratosis • Bowen disease (SCC in situ) • Invasive SCC / SCC in situ • Lentigo maligna • Malignant melanoma • Pigmented basal cells • Verruca vulgaris (warts)	• Acrochordon (skin tags) • Acrokeratosis verruciformis • Benign lichenoid keratosis • Condyloma acuminatum • Eccrine poroma/hidroacanthoma simplex • Melanocytic nevus • Solar lentigo (liver spots) • Tumor of the infundibulum

SCC=squamous cell carcinoma.

A Closer Look at Seborrheic Keratosis

Since its introduction in 1998, the dermatoscope has changed the landscape of dermatology. The device's sensitivity is 95.7%, and its specificity is 78.3%.¹⁰ In a study of 134 cases of melanoma that resembled SK, dermoscopy demonstrated its efficacy in finding 82% of SK-like melanomas in patients initially misdiagnosed with SK.¹⁰ Among the findings was that a blue-black sign aided in the correct diagnosis of melanoma in distinguishing it from SK.¹⁰

be helpful for ascertaining the correct diagnosis. Dermoscopy is >4 times more accurate than examination with the naked eye.⁹

Use of a dermatoscope, following proper training, reduces misdiagnoses and unnecessary biopsies. However, not all dermatology residents have access to adequate dermoscopy training.¹¹ The triage amalgamated dermatoscopic algorithm (TADA) method—in which clinicians first decide whether a lesion could be malignant—was shown to significantly increase the number of correct diagnoses of benign lesions.¹² The most important decision is to determine whether a lesion is benign or malignant; if it is the latter, the clinician should obtain a timely biopsy.¹²

If a misdiagnosis occurs, the delay in treatment, or the use of an inappropriate treatment, can mean the difference between life and death. In some cases, for example, a patient who has hidroacanthoma simplex (HAS; also known as intraepidermal eccrine poroma) may be misdiagnosed as SK. Inappropriately treating the HAS lesion with cryotherapy (liquid nitrogen) could trigger a rare but potentially fatal porocarcinoma.¹³

Indications for Biopsy

Most SK lesions can be readily diagnosed on visual and tactile examination, but if there is doubt—or it takes more than a minute to discern whether it is a seborrheic keratosis—consider a shave biopsy.¹ Clinicians who are not dermatologists tend to perform excisional biopsies—involving a larger area of the skin—at a rate 5 times that of dermatologists.¹ On average, dermatologists see more than 150 SK lesions per month, so they are well equipped to diagnose the lesions quickly and efficiently with the aid of a dermatoscope.²

To Treat or Not to Treat?

Understandably, patients' concerns that their SK lesions might be malignant will often lead them to see their dermatologist. Many complain that the lesions—which are sometimes called “senile barnacles”—make them appear older.

In most cases, SK lesions do not require medical treatment. The decision to treat is based on several factors. SK should be treated if the lesion treatment is inflamed, irritated, itchy, or (rarely) painful due to friction (eg, from clothes, razors, or jewelry). In such cases, treatment should be covered by medical insurance. In a survey of 594 patients, 19% presented with SK lesions that were irritated.² However, in 43% of the cases, patients requested the removal of unsightly SK lesions because they were located in cosmetically sensitive areas, such as the face and neck.^{1,2} As a rule, patients must cover the cost of such removal as an out-of-pocket expense.

Often, when patients hear that insurance will not reimburse for a cosmetic procedure, they may decide not to have the lesions removed.² Of the patients who choose removal, most are women, and most of the lesions appear on the face.² Clinicians should be prepared to counsel patients on their treatment options.

Treatment Options

How to remove an SK lesion depends largely on whether the clinician suspects a malignancy, which would need to be biopsied for further inspection.^{1,2} Other factors that guide the decision on which modalities to use are the location of the lesion(s) on the body, the patient's pigmentation, and the

thickness and size of the lesion.¹ Lesions in cosmetically sensitive areas call for a conservative approach.

Cryosurgery

There are no guidelines or efficacy studies on the best way to remove SK lesions. Approximately two thirds of dermatologists prefer cryosurgery with liquid nitrogen, which can be performed in the office, generally without a topical anesthetic.^{1,2} Cryosurgery is thought to freeze the SK cells to a temperature of -20°C to -30°C (-4°F to -22°F) so that they dehydrate and eventually slough off.¹ There are no standards for the duration of cryosurgery applications, whether directly or with a cotton swab. The American Academy of Dermatology recommends that any clinician using this technique be properly trained.¹

Each lesion has a variable treatment course. A typical, flat SK lesion may need only a single application of 5 to 10 seconds of liquid nitrogen, whereas a larger, thicker lesion may require several freeze/thaw cycles and multiple office visits.¹

The benefits of cryosurgery include low infection risk, ease of application, and minimal scarring.¹ Should the area ulcerate, proper healing can be promoted by keeping the treatment area clean, moist (with an ointment such as petrolatum), and covered.¹ Cryosurgery lesions take approximately 7 to 10 days to heal, but the SK lesion itself may not slough off for a few weeks, depending on the thickness.¹ In a study of 80 patients, most preferred cryosurgery because the wound care was not as extensive as it was for curettage or excision.¹

Potential disadvantages of cryosurgery include edema, erythema, scarring, and hypopigmentation, particularly in sensitive areas. Some clinicians may be too aggressive when using this approach for treatment.¹ A few patients might find cryosurgery too painful; in others, erythema and swelling might persist for a few weeks.¹ Relative contraindications for cryosurgery include lesions near the eyes and in patients subject to postinflammatory hyperpigmentation. Avoid freezing suspicious lesions requiring biopsy such as melanoma, basal cell carcinoma, or squamous cell carcinoma.¹

Curettage

Curettage of SKs can be performed efficiently without anesthesia, although many patients find this approach unacceptable.¹ Use of anesthesia usually keeps the patient comfortable during the procedure. The benefit of curettage is that patients leave the clinic free of the treated lesions. However, there is usually some bleeding, and complete healing takes 5 to 7 days. Curettage can be used as a stand-alone method or it can be combined with cryosurgery for treating deeper lesions.¹ It can be more time-consuming than cryosurgery and does require the use of a curette, but generally the wounds heal without scarring.¹ Curettage is the preferred approach of many dermatologists, including the authors of this article.

Shave or Surgical Excision

In the case of a potentially malignant lesion, shave removal and biopsy of the SK lesion will preserve the tissue for further histopathologic inspection.¹ Surgical excision of an obvious SK lesion is generally unnecessary and should be avoided. Treatment depends on the thickness and location of the lesion and whether multiple lesions are present.¹

Electrosurgery

Coagulation of SKs by electrodesiccation or electrocautery involves destruction of small lesions by cold point diathermy or heat, respectively.¹ Electrodesiccation requires contact of an RF electrode with the skin, whereas electrofulguration destroys superficial lesions by “sparking” the affected area.¹ Electrocautery uses a red-hot filament. Electrosurgery is often the preferred method for removing dermatosis papulosa nigra lesions, especially when the patient is concerned about pigment changes.¹ However, there are numerous ways of treating this condition, including the use of lasers.

Lasers

Both ablative (eg, CO₂ and erbium-YAG) and nonablative (eg, 755-nm alexandrite and 532-nm diode) lasers have been used to remove SK lesions with varying results. Much depends on the training and comfort level of the clinician. As is true of cryosurgery, in the absence of guidelines, the clinician's experience determines the intensity and duration of laser treatment.¹ Noninvasive treatment using intense pulsed light (IPL) to treat SK lesions has been tested in 10 case studies (mean age, 61.7 years) with positive results, albeit with small, superficial thin lesions.¹⁴ The lesions "disappeared" (became depigmented) in an average of 2 treatments within 30 days without scarring or erythema. Researchers caution that results can vary according to the clinician's experience with IPL.

Topical Agents on the Horizon

The need exists for an effective noninvasive treatment to remove SK lesions.¹⁵ There are currently no topical treatments approved by the US Food and Drug Administration (FDA) for SK. However, several such therapies are in development.

Preliminary evidence shows promise for an agent in development, a high-concentration hydrogen peroxide topical known as A-101 40% solution (A-101), which must be applied by a healthcare provider as an in-office procedure.¹⁶ In 2 pivotal phase 3 trials (N=937), 51.3% of SK lesions treated with A-101 were assessed as clear or near clear compared with 7.3% in the placebo group.¹⁶⁻¹⁸ For facial lesions, A-101 cleared 65.3% of SK lesions vs 10.5% for placebo. Local skin reactions, such as hypopigmentation, hyperpigmentation, and scarring, were graded as mild.¹⁶ An open-label study evaluating safety in 147 patients has been completed.¹⁹ A new drug application for A-101 has been submitted to the FDA for review; a decision is expected by the end of 2017.

Another topical formulation being investigated is potassium dobesilate 5% cream, which inhibits the skin's FGFR3 activity to halt SK lesion formation.²⁰ In a case report, topical dobesilate demonstrated efficacy for facial SK with a 6-month patient application, even at the 1-year follow-up.²⁰ Adverse events, such as application-site reactions, skin atrophy, dyspigmentation, or skin thinning, were not reported in this case study. Topical dobesilate may provide another modality for SK lesion removal in cosmetically sensitive areas.²⁰

The nonsteroidal anti-inflammatory drug diclofenac gel 3% showed promise in a case study of a 73-year-old man with an SK lesion on his nose

in which the gel applied twice daily dissolved the lesion within 30 days.²¹ Though diclofenac gel is FDA-approved for clearing actinic keratosis, it may provide another (off-label) option for those whose SK lesions are in cosmetically sensitive areas.

In addition, BL-5010, a combination of aqueous trichloroacetic acid and formic acid, is a topical formulation applied with a pen device to target SK lesions.²² In phase 1/2 trials with 60 patients, 1 application of the formulation eradicated 96.7% of the lesions in 2 weeks.²³

In an open-label study of 15 patients with SK, tazarotene 0.1% cream applied twice daily disintegrated the lesions within 16 weeks.¹⁵ Twice-daily tazarotene 0.1% cream was preferred by patients and was more effective than daily applications of its comparators, calcipotriene 0.005% ointment and imiquimod 5% cream, which did not yield any clinical improvement.¹⁵

Topical and systemic vitamin D have been studied as options for eradicating SK, but neither strategy has had much success.²⁴ In a study of 116 cases, topical vitamin D eliminated >80% of the SK lesions in 30.2% of patients.²⁵ However, SK lesions tended to recur after the use of either formulation of vitamin D.

Preliminary in vitro trials have provided evidence for 2 investigational topicals that rely on Akt inhibition, A-443654 and GSK690693.⁶ In these trials, lesions exposed to A-443654 completely disappeared.⁶

The emergence of novel noninvasive and topical formulations will provide patients and clinicians with more cosmetically elegant solutions for destroying SK lesions without scarring, dyspigmentation, or infection.

Summary

SK is a common dermatologic condition, particularly in persons older than 50 years. It is incumbent upon clinicians to accurately diagnose SK lesions before removing them. These SK lesions are usually benign and can be removed for cosmetic reasons if the patient desires; treatment may be indicated (and may be reimbursable) if the lesion is irritated. In the case of suspicious lesions, clinicians should perform a shave biopsy to ensure that the lesions are not premalignant or malignant, such as melanoma. Choice of treatment is based mainly on the number of lesions, location on the body, skin pigment, thickness of the lesion, and patient esthetics. Emerging topical therapies may be found to offer effective lesion removal without the use of cryotherapy, lasers, or other standard modalities. ■

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