Improve Your Diagnostic Skill

Here's practical advice on recognizing SK subtypes and identifying potentially dangerous mimickers, based on a study of 232 cases.

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Among the most common benign skin neoplasms that affect the skin of older individuals, seborrheic keratoses are classically tan or brown, plaque-like with a verrucous surface and a "stuck on" appearance. They usually occur on the face, neck, trunk, and arms.[1] Sometimes seborrheic keratoses display an irregular shape, and a variety of brown and black colors can occur within the same lesion, leading to difficulty differentiating this benign neoplasm from life threatening malignant melanoma.[2] In histopathological terms, a seborrheic keratosis often demonstrates papillomatosis, hyperkeratosis, acanthosis, and pseudo-horn cyst formation. This article will explore the clinical and histopathological features of all varieties of SKs and consider the features of four significant imitators of SKs in order to aid diagnosis and treatment.

Our recommendations are based on the largest series of seborrheic keratoses studied with regards to clinical and histopathologic features. The vast majority of SKs were not biopsied or treated in any manner. Reassurance is usually sufficient when lesions are asymptomatic and diagnosis is certain based on clinical features. Clinically unusual, irritated, or cosmetically bothersome SKs are generally treated with liquid nitrogen cryosurgery.

Classifications

Seborrheic keratoses are classified on both clinical and histopathological features as adenoid, irritated, clonal, acanthotic, hyperkeratotic, stucco keratosis, pedunculated, and dermatosis papulosa nigra.[1] The first type of SK is the adenoid or reticulated type (Figure 1a). On histopathologic examination, lesions display thin strands of epidermal cells extending down from the epidermis and subsequently interweaving and branching into the dermis (Figure 1b). Pseudo-horn cysts usually are not present in the adenoid type, and these lesions may have a shiny, less verrucous surface.[3] Heavy pigmentation is found in the basaloid cells, and some authorities feel these lesions may evolve from solar lentigenes.[4] This is in part because the elongated rete pegs of a solar lentigo resemble the more pronounced elongated and anastomosing rete pegs of an adenoid seborrheic keratosis. In fact, some adenoid SKs show foci indistinguishable from solar lentigenes.

Irritated or inflamed seborrheic keratoses (Figure 2a) prominently display whorls of eosinophilic squamous cells in an onion-peel arrangement, which can resemble the horn pearls of squamous cell carcinoma. In addition to acanthosis and pseudo-horn cyst formation, irritated SKs show spongiosis, scale crusting, dermal inflammation, and exocytosis of acute and chronic inflammatory cells (Figure 2b).[1] The squamous eddies are also seen in the irritated SKs and they often lack the number of horn cysts found in other SKs.[5] In some cases this "squamatization" seen on histopathological examination can mimic squamous cell carcinoma.

Clonal seborrheic keratoses (Figure 3a) are another subtype, characterized by "nests" of basaloid keratinocytes with distinct

features that are different from the surrounding epidermis. The "clonal" foci demonstrate uniformly darkly stained nuclei (Figure 3b).[1] In some instances these cells can be can be quite immature and may resemble basal cell carcinoma.[5] Like other SKs, these lesions show hyperkeratosis and acanthosis. We identified only a few of these lesions in our series; no specific clinical features discovered would distinguish this variant from other SKs.

Acanthotic seborrheic keratoses (Figure 4a) constitute the most common category of SKs and are characterized by numerous pseudo-horn cysts and absent to slight hyperkeratosis and papillomatosis. The epidermis is greatly acanthotic and has a straight lower margin which correlates with the "stuck on" appearance noted clinically (Figure 4b).[5] These lesions can be dark in color, though many are tan or brown. There is also evidence of true horn cysts, which begin as areas of orthokeratosis that fuse with the invaginations of the surface keratin. The acanthotic epidermis often contains more basaloid cells than squamous cells, and there is usually an increased amount of melanin in the keratinocytes located at the dermal-epidermal junction.[3] Occasionally, a bandlike lymphocytic infiltrate can be seen in the upper dermis underlying an acanthotic seborrheic keratosis.[1]

Hyperkeratotic seborrheic keratoses (Figure 5a) differ from other types because they display pronounced hyperkeratosis and papillomatosis. There is only minimal acanthosis. The term "church spires" has been used to describe the papillomatous projections of epidermal lined papillae (Figure 5b).[3] Clinically, these verrucous lesions often appear "dried up" and show regular borders and a "stuck on" appearance. The base of the lesion is flat and as a rule there is minimal pigment deposition. The hyperkeratotic type sometimes is indistinguishable from acrokeratosis verruciformis of Hopf when it comes to histological inspection.

Stucco keratoses, a clinically distinct variant of seborrheic keratosis, demonstrate a histological pattern similar to the hyperkeratotic type. They appear clinically as white to gray 1-3mm "stuck on" hard plaques that usually affect the lower extremities, classically the ankle (Figure 6a & 6b). Though reported to affect the upper extremities, they tend to spare the palms. Scraping off these lesions will result in only minimal bleeding. Older males are affected more with stucco keratosis, and some authorities believe there is a relation between heat and chemical exposure.[3,6]

The pedunculated type of seborrheic keratosis is a lesion that most commonly affects the eyelids, neck, and axillae (Figure 7a). They demonstrate an acanthotic and hyperpigmented epidermis overlying a pedunculated lesion, usually between 2-8mm in diameter. The dermis is made up of attenuated collagen and dilated blood vessels often with trapped erythrocytes (Figure 7b).[6]

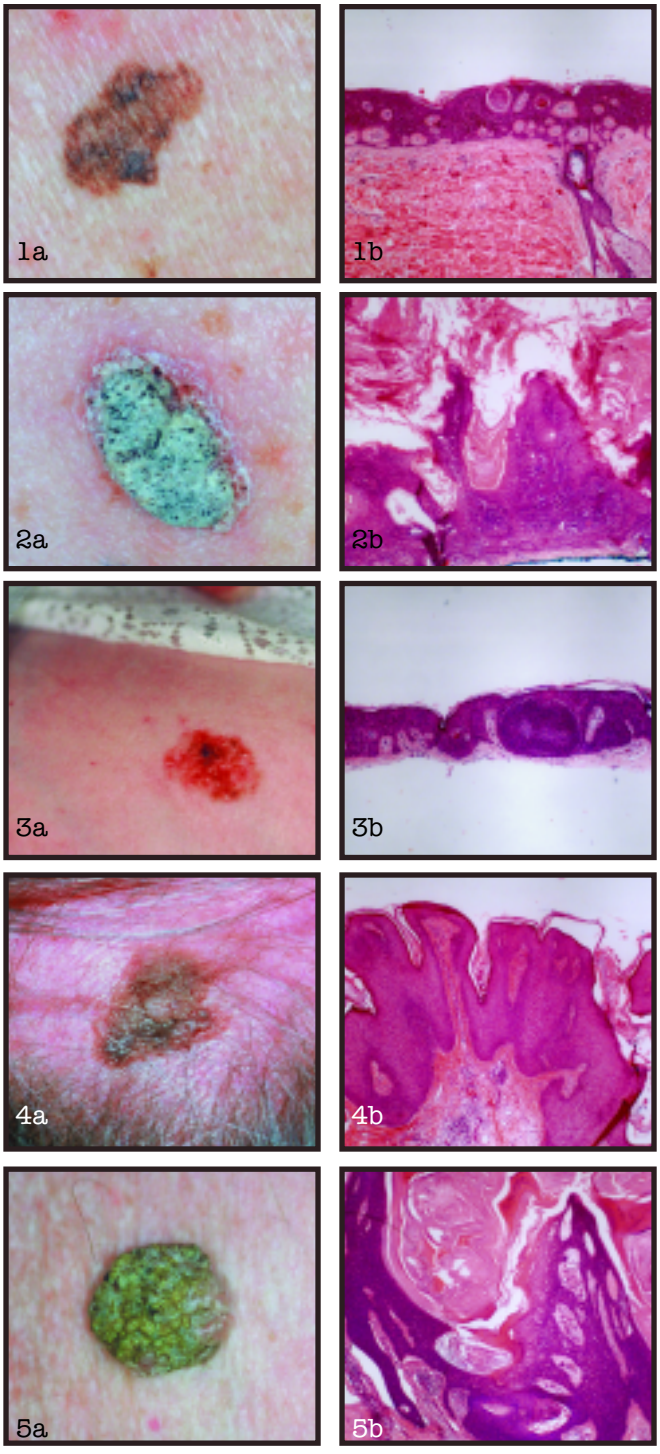
Another variant of seborrheic keratosis is dermatosis papulosa nigra. These lesions tend to occur in dark skinned individuals. They appear mostly on the face but can also appear on the neck and trunk. They are small, heavily pigmented papules (Figure 8a). It is not uncommon to find numerous papules on affected persons. Histologically, they resemble seborrheic keratosis of the acanthotic type (Figure 8b). However, lesions of dermatosis papulosa nigra are smaller than most SKs. They also show heavy pigmentation and numerous pseudo-horn cysts.[3]

Of special mention is the occurrence of multiple, often pruritic seborrheic keratoses erupting over a short period of time in association with internal malignancy. This "syndrome," first mentioned in 1890, is the sign of Leser-Trelat. The most commonly associated internal malignancies are breast, colon, and stomach. However, since SKs are common, and the previously mentioned cancers are common, there is real debate as to the significance of this sign. Many authors conclude that this sign is just coincidence while others recommend a search for internal malignancy when multiple SKs appear suddenly.[7,8]

Because of the potential for metastasis, any seborrheic keratosis-like lesion with any likelihood of melanoma requires biopsy. Histolopathologic differentiation of these two lesions is straightforward.

Spotting SK Mimickers

At least four significant skin lesions can clinically resemble seborrheic keratoses: malignant melanoma, verruca vulgaris, compound nevi, and linear epidermal nevus. Malignant melanoma is clinically assessed using the ABCDEs. It is frequently an asymmetric lesion with an irregular or notched border that can show a variety of colors, such as browns, reds,



black, blues, and grays; the diameter of a melanoma is usually greater than 6mm and these lesions have the potential to become quite large.[2] Enlargement and other changes in shape, color, crusting, symptomatology (pain, pruritus), or ulceration can be the first clue to the diagnosis of melanoma.[9] One study found a prevalence of 0.66% of melanoma in cases submitted for histopathologic analysis with a clinical diagnosis that included SKs. The authors investigated clinical records and determined half of the cases represented true clinical diagnostic errors.[10] Therefore, it is not difficult for the clinician to diagnose SKs in lesions that in reality are malignant melanoma.

Likewise, seborrheic keratosis can resemble melanoma (Figure 9a & 9b). Because of the potential for metastasis, any seborrheic keratosis-like lesion with any likelihood of melanoma requires biopsy. Histolopathologic differentiation of these two lesions is straightforward. Melanoma shows irregular nesting of atypical melanocytes with nuclear atypia and "pagetoid" infiltration of the epidermis. Pigmented basal cell carcinoma can also resemble seborrheic keratosis, though they are usually pearly and prone to ulceration (Figure 10a). Again, histopathology readily differentiates these lesions, which show masses of basaloid tumor cells (Figure 10b).

Of less clinical significance, a number of benign lesions can resemble SKs. The most common of these are verruca vulgaris and condyloma acuminata or genital warts (Figure 11a). On histological examination there is acanthosis, papillomatosis, and hyperkeratosis. These features could also be seen in seborrheic keratoses; however, a marked vacuolization of cells and a layer of hypergranularity is seen in viral warts (Figure 11b).[12, 13, 14] Rarely when the distinction between a wart and a SK has clinical significance, HPV marker studies can help distinguish between these lesions.

Compound nevi, blue nevi, and sometimes congenital nevi can simulate seborrheic keratoses because of their dark coloration and shape. Compound nevi are elevated lesions 1-5mm in diameter that can also be papillomatous in nature (Figure 12a & 12b). Blue nevi are similar in size but often show a dark blue or black coloration (Figure 13a & 13b). Congenital nevi form plaques that can be much larger, show homogenous brown coloration, and sometimes have dark hair emanating from the surface (Figure 14a & 14b). Therefore, it is easy to mistake nevi for small seborrheic keratoses and vice-versa. As is the case with the other clinical simulators of seborrheic keratosis, histological examination can readily differentiate between the two. Compound nevi histopathologically demonstrate nevus cells in

1a. Adenoid SK. Note variegation in color in 1.7cm irregularly pigmented lesion present for two to three months; resembles superficial spreading MM. **1b.** Areas with more and less intense melanin deposition correlate with clinical appearance. (H&E 40x) **2a. Irritated SK.** 1.4 x 0.9 x 0.6mm lesion present for several months on the upper back shows marked scale crusting and irritation; was irritated by patient's bra. **2b.** Note acanthosis, scale crusting, squamous eddies, underlying inflammation. (H&E 40x) **3a. Clonal type SK.** Erythematous, verrucous surface with flecks of darker pigmentation. **3b.** Islands of round basaloid "clonal" keratinocytes stain more darkly than surrounding keratinocytes. (H&E 40x) **4a. Acanthotic AK.** 2.0 x 1.7 x 0.4cm verrucous lesion with some variegation in color on the apical scalp of an elderly patient. **4b.** Marked acanthosis and papillomatosis with minimal hyperkeratosis. (H&E 100x) **5a. Hyperkeratotic SK.** 1.7 x 1.7 x 0.7cm lesion on the thigh appears "dried up" and demonstrates classic "stuck on" appearance. **5b.** Pronounced hyperkeratosis and papillomatosis are

nests in both the dermis and the dermal-epidermal junction demonstrating vertical maturation.[11] Blue nevi show dendritic melanocytes with adjacent melanin laden macrophages within the dermis.

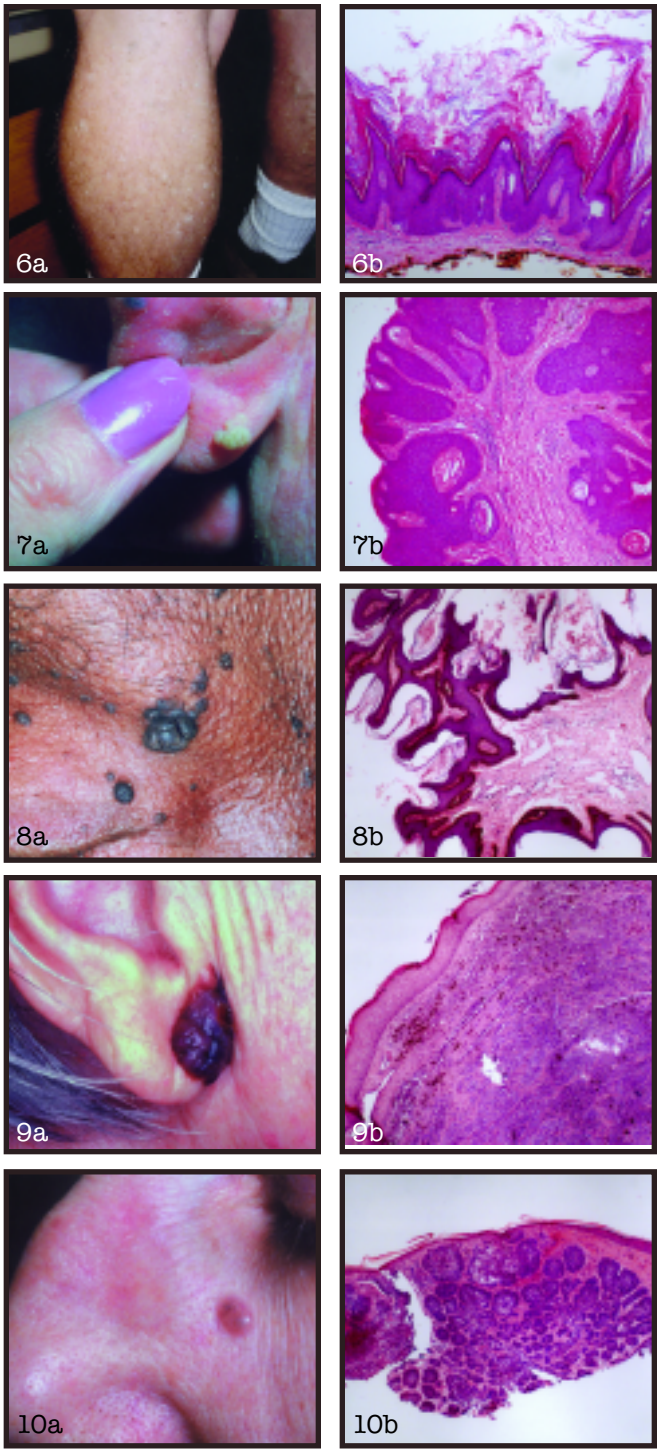
Finally, just as the three previous lesions can simulate a seborrheic keratosis, linear epidermal nevi can mimic seborrheic keratosis both clinically and histopathologically. Linear epidermal nevus can be localized or systematized. The localized type appears as a linear lesion, is usually present at birth, and is composed of closely approximated tan to brown, verrucous papules. They occur in the same areas of the skin affected by seborrheic keratosis: arms, trunk, head (Figure 15a & 15b). The systematized type differs in that there are numerous linear lesions often in parallel. Upon histopathological inspection, linear epidermal nevi display acanthosis, papillomatosis, hyperkeratosis, and lengthening of the rete ridges.

Since these are features of a benign papilloma they can easily be confused with an SK. However, in certain cases of linear epidermal nevi, these lesions can display a histologic feature known as epidermolytic hyperkeratosis. This finding consists of four components: perinuclear vacuolization of cells in both the stratum spinosum and granulosum, keratohyaline granules that are increased in number and irregularity, irregular cell boundaries around the areas of vacuolization, and dense hyperkeratosis in the stratum corneum.

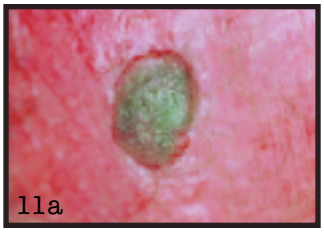
To differentiate linear epidermal nevus from the hyperkeratotic type of SKs, there must be an absence of horn cysts and basaloid cells, and the papillae must extend upward.[1,15] Seborrheic keratosis mimicking LEN is also possible (Figure 16a and 16b).

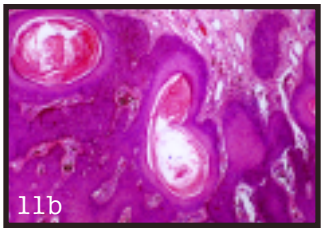
Conclusion

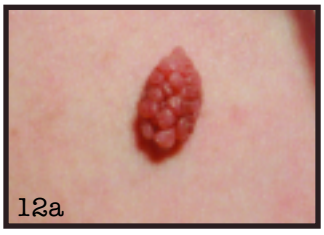
There are at least eight subtypes of seborrheic keratosis and at least four skin neoplasms that resemble SKs. Clinicians must maintain a high index of suspicion for malignant melanoma and basal cell carcinoma when diagnosing SKs. Since it is practically impossible to biopsy all seborrheic keratoses, the physician should employ the ABCDEs of malignant melanoma and the "ugly duckling" sign (peculiar or dissimilar appearance of a lesion compared to surrounding lesions[16]) to differentiate between a seborrheic keratosis and a melanoma and carefully analyze pigmented lesions for pearliness and ulceration typical of pigmented basal cell carcinoma. Dermoscopy can help differentiate between a SK and a melanoma. Following certain criteria, the "dermoscopist" can

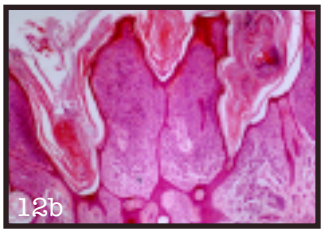


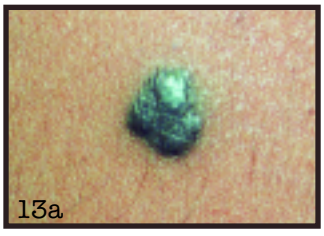
characteristic of hyperkeratotic SKs. (H&E 100x) **6a. Stucco keratosis.** Scores of whitish-gray plaques over the ankle and dorsum of the foot. **6b.** Church-spire like projections with hyperkeratosis. **7a. Pedunculated SK.** Lesion on the ear of elderly patient was bothersome when bumped. **7b.** Lesion shows otherwise typical features of SK. **8a. Dermatosis papulosa nigra.** Variant of SK is found in dark skinned individuals. Multiple black papules were present on the temples. Dozens of similar lesions were present on the cheeks. **8b.** Note small discrete lesion with acanthosis, hyperkeratosis, and pseudo-horn cyst formation. (H&E 40x) **9a. Nodular malignant melanoma.** Simulates an SK with little horizontal growth. Hutchinson's sign is subtle but present with a small amount of macular pigmentation at the edge of nodular portion. **9b.** Histology. **10a. Pigmented BCC.** Tan coloration clinically simulates SK. **10b.** Micronodular masses of basaloid cells with peripheral palisading within the dermis. Melanin deposition within tumor contributed to clinical appearance. (H&E 40x)

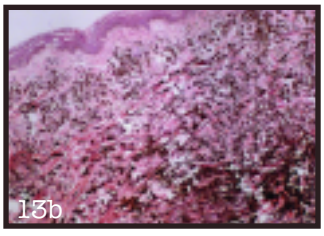


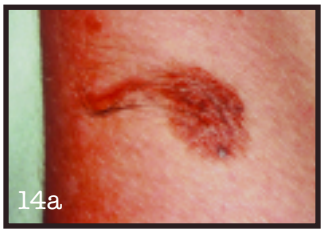


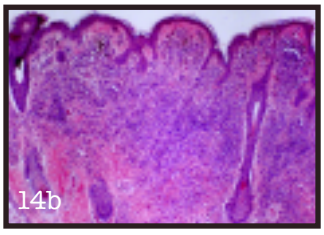


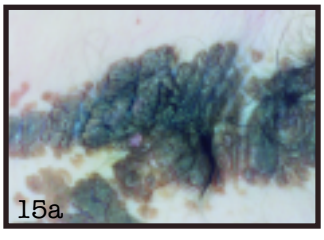


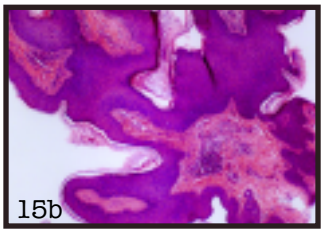


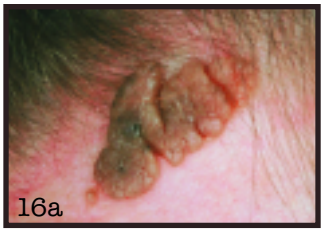


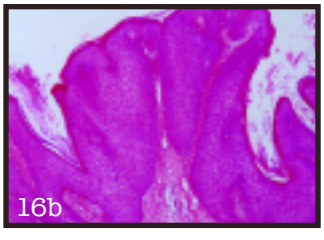












look for milia-like cysts, comedo-like openings, fissures, hairpin blood vessels, and network-like structures typical of a seborrheic keratosis.[17,18] Dermoscopy of a malignant melanoma would reveal atypical pigment network and a blue-white veil appearance.[19] Of course, any doubt about any pigmented lesion's benignity warrants excision of the lesion. If a presumed seborrheic keratosis does not respond to liquid nitrogen cyrotherapy, consider a biopsy to provide a definitive diagnosis.

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11a. Condyloma accuminatum. 1.2 x 1.0cm crusted brown lesion on the scrotum clinically could represent irritated viral wart or irritated SK. **11b.** Acanthosis, pseudo-horn formation, and melanin deposition. Other areas show hypergranulosis with vacuolization typical of viral wart. (H&E 100x) **12a. Compound nevus.** 12 x 5mm "cauliflower-like" appearing lesions with brown coloration mimics SK. **12b.** Nevus cells present at dermal-epidermal junction and within dermis. Papillomatosis contributes to "cauliflower-like" appearance. (H&E 100x) **13a. Blue nevus.** 9 x 7mm jet black nodule, regular border, difficult to diagnose clinically. Differential included blue nevus, pigmented Spitz nevus, and nodular MM. **13b.** Hyperpigmented melanocytes and melanophages present within round nodule. (H&E 40x) **14a. Congenital nevus.** 2.0x 1.6cm brown plaque shows dark hair emanating. **14b.** Histopathology. **15a. Linear epidermal nevus.** 18 x 3cm linear lesion with verrucous features. **15b.** Acanthosis, hyperkeratosis, and marked papillomatosis produce verrucous appearance. (H&E 40x)

The Study At-a-Glance

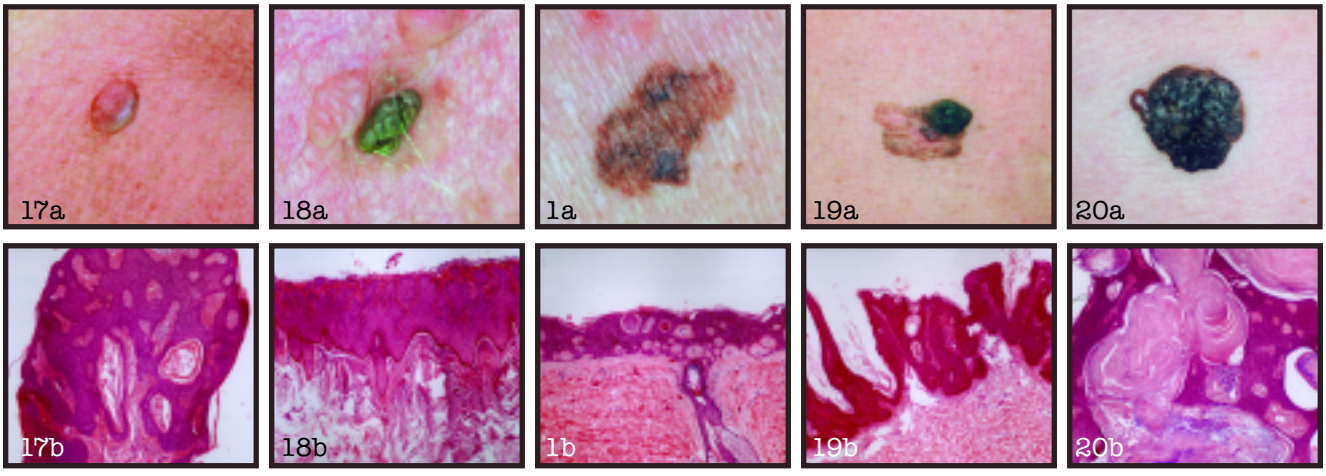
We identified all cases of seborrheic keratoses for which biopsy material was available over 18 years in a single private practice (RTB). Clinical images of these lesions were available. Clinical photos, H&E slides, and pathology reports were retrieved, organized, and reviewed. Since liquid nitrogen cryotherapy, a common treatment for SKs, produces no histologic specimen, cases treated with cryotherapy were not included. The study cases are a distinct minority of all SKs identified in this practice and represent lesions which were bothersome to patients and/or not amenable or resistant to previous cryotherapy. In many cases, the diagnosis was in doubt. With these limitations in mind, a careful analysis of this data led us to validate and extend information about these common lesions.

A total of 240 cases of SKs were identified within the full data set; eight were removed from the study due to poor clinical photo quality. The remaining 232 SKs were classified using both clinical and histopathological criteria into the following categories: 100 (43.1%) irritated; 66 (28.4%) acanthotic; 19 (8.2%) pedunculated; 16 (6.9%) hyperkeratotic; 10 (4.3%) adenoid; six (2.6%) features of both seborrheic keratosis and verruca vulgaris; five (2.2%) melanoacanthoma; four (1.7%) early lesions; three (1.3%) dermatosis papulosa nigra; two (0.9%) clonal; one (0.4%) stucco.

Twenty biphasic lesions were identified showing two portions of the same lesion that were clinically distinct from each other. Seven of these showed scale crusting overlying one portion of the lesion; four lesions had foci with more marked acanthosis in one area; four lesions showed portions that were pedunculated or sessile at one pole (Figure 17a & 17b). In addition, some biphasic lesions showed combinations of two distinct histologic patterns of seborrheic keratosis. Of these, three showed a combination of hyperkeratotic and acanthotic features; one showed hyperkeratotic and adenoid foci (Figure 18a & 18b). Finally, one hyperkeratotic seborrheic keratosis displayed dense pigmentation in the keratin layer restricted to one focus of the lesion.

The data set included eight SKs that clinically resembled malignant melanoma. Four of these suggested a diagnosis of superficial spreading malignant melanoma. The variegation of color in these lesions was correlated with variation in the density of melanin pigmentation within one adenoid SK (Figure 1a & 1b); varying degrees of acanthosis were present within three cases (Figure 19a & 19b). Four cases suggested nodular melanoma. Under histopathologic inspection two of these lesions showed marked hyperkeratosis, papillomatosis, and acanthosis (Figure 20a & 20b), one lesion showed adenoid features with scale crusting, and the third showed irritation with thick scale crusting.

Eight cases studied were clinically dark black but did not clinically resemble malignant melanoma. All of the lesions demonstrate pronounced lentiginous melanocytic hyperplasia. One lesion showed dense lentiginous melanocytic hyperplasia without melanin deposition elsewhere. Two lesions showed additional melanin within higher levels of the epidermis. Five lesions revealed additional marked pigmentation within dermal melanophages. Two of these latter lesions showed considerable hyperkeratosis, which could also have contributed in part to the dark coloration.



16a. Acanthotic SK. Acquired lesion clinically resembles linear epidermal nevus. **16b.** Hyperkeratosis, papillomatosis, and acanthosis identify an SK. **17a. Biphasic appearing SK.** The sessile nature of the lesion leads to a darker appearance on the right side because the epidermis is layered on top of itself. **17b.** Darker pole of lesion produced by "double" thickness of the epidermis. (H&E 40x) **18a. Biphasic appearing SK.** Lesion is biphasic due to presence of adjacent SKs with entirely different clinical features. **18b.** Two histopathologic patterns: adenoid on the left two-thirds and hyperkeratotic on the right one-third. (H&E 40x) **19a. Acanthotic SK.** Variegation of color resembles nodular MM. **19b.** Thicker portion correlates with dark brown coloration clinically. (H&E 40x) **20a. Hyperkeratotic SK.** Dark black verrucous appearance with variegation of color and a shiny papule at the pole suggested irritated nodular melanoma. **20b.** Marked hyperkeratosis, acanthosis, and papillomatosis. Lesion thickness, melanin deposition, and marked hyperkeratosis contribute to black color and variation in color. (H&E 100x)