

Seborrheic keratosis

Epidermal neoplasm: pathogenesis, morphology and diagnostic interpretation

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Learning outcomes

- Distinguish benign epidermal keratinocytic lesions from melanocytic lesions.
- Explain the proposed role of activating FGFR3 mutations.
- Recognize macroscopic and microscopic features of seborrheic keratosis.
- Relate keratin-filled structures to dermoscopic appearances.
- Identify diagnostic mimics and interpret eruptive lesions cautiously.

Epithelial rather than melanocytic

- Seborrheic keratosis is an epidermal keratinocytic tumor.
- Pigmentation reflects melanin within proliferating basaloid cells.
- Dark coloration alone does not establish melanocytic origin.

Cell of origin

**Epidermal
Keratinocyte**

Melanocyte

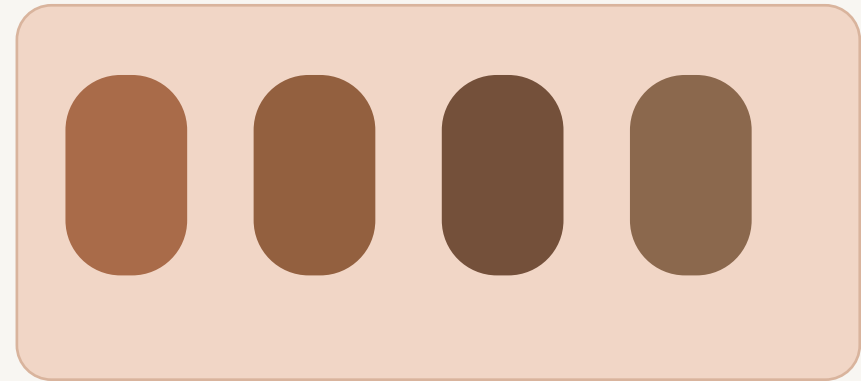
Seborrheic keratosis

Melanocytic nevus

Original editable schematic; Not a clinical or histologic specimen

Why a brown lesion can mislead

- Both keratinocytic and melanocytic lesions may be pigmented.
- Clinical appearance must be interpreted with surface texture and architecture.
- An atypical lesion cannot be declared benign on color alone.



Keratinocyte tumor can contain melanin

Original editable schematic; Not a clinical or histologic specimen

Definition and biological behavior

- A common benign epidermal tumor of keratinocytes.
- Usually presents as a discrete plaque or papule on the skin surface.
- Growth is typically exophytic and well circumscribed.
- Clinical significance is primarily recognition and exclusion of mimics.

Typical age distribution

- Most frequently encountered in middle-aged and older individuals.
- Age supports but does not establish the diagnosis.
- A new pigmented lesion still requires appropriate morphologic assessment.

**Middle-aged
And older adults**

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Usual anatomical distribution

- Lesions are especially common on the trunk.
- Head and neck may be affected.
- Extremities also develop seborrheic keratoses.
- Site is contextual evidence, not a definitive criterion.

**Trunk → head / neck
→ extremities**

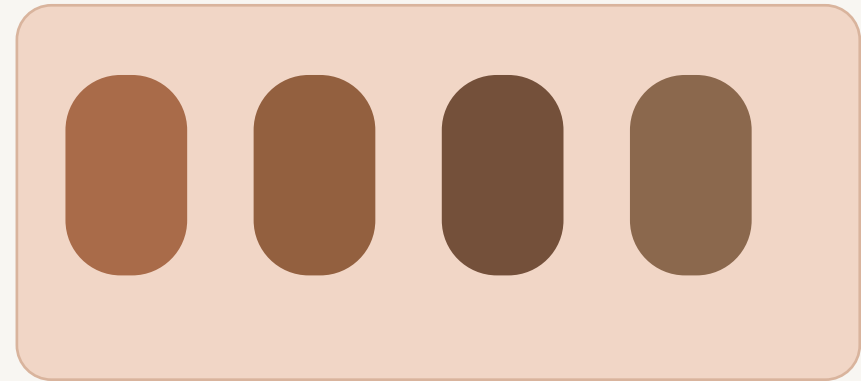
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Single versus multiple lesions

- Seborrheic keratoses may be solitary or numerous.
- A group of clinically similar plaques can be reassuring but not diagnostic.
- Evaluate a morphologically different or changing lesion independently.

The “stuck-on” clinical impression

- A sharply bordered plaque seems attached to the skin surface.
- Exophytic architecture provides a histologic correlate.
- The impression is a useful clue, not a stand-alone rule-out test for melanoma.

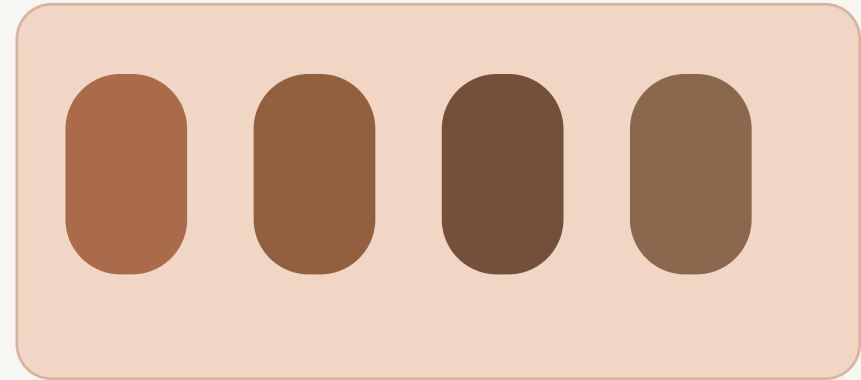


Raised, sharply edged epidermal plaque

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Shape, contour and borders

- Classic lesions are round to oval.
- They are generally well demarcated from adjacent skin.
- Surface relief can be flat or elevated.
- Irregular clinical lesions warrant greater diagnostic caution.

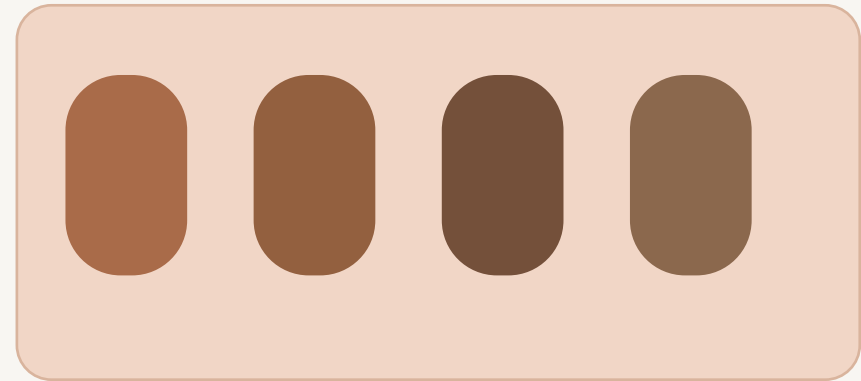


Well-circumscribed clinical outline

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Waxy, velvety or granular surface

- The lesion surface may appear waxy.
- Velvety or granular texture is characteristic.
- Abundant surface keratin helps explain the texture.

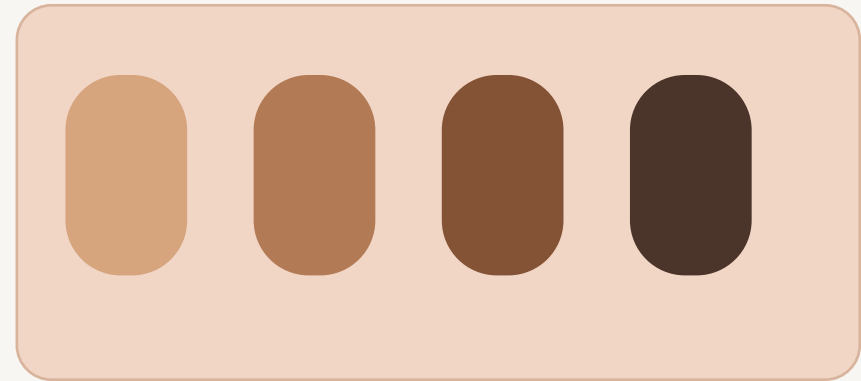


Textured, keratinizing upper surface

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A broad spectrum of coloration

- Typical colors span tan to dark brown.
- Variable melanin is present in basaloid tumor cells.
- Pigmented seborrheic keratosis can resemble melanocytic lesions.



Variable pigment intensity

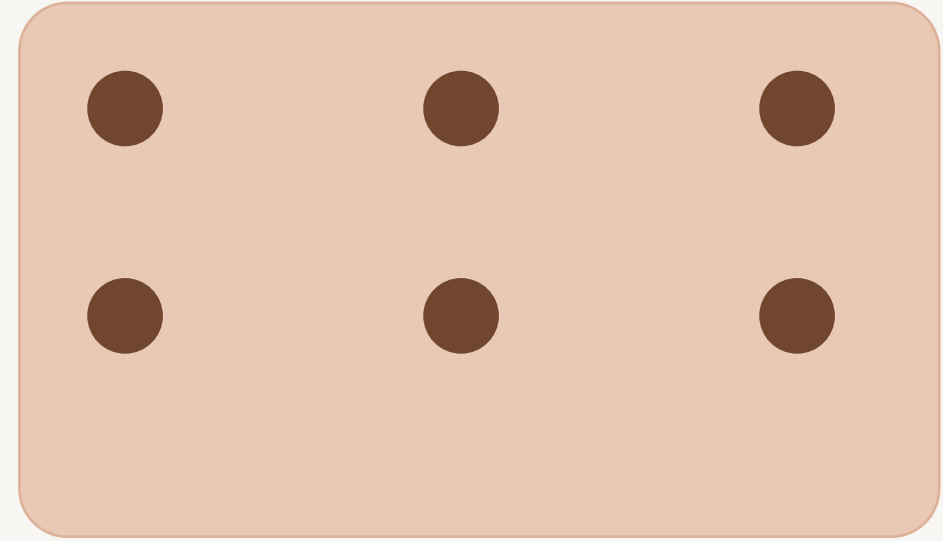
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Dimensions and morphology

- Diameter ranges from millimeters to several centimeters.
- A larger lesion can remain benign; Size alone does not define malignancy.
- Assess the full pattern: Contour, pigment, surface and trajectory.

Keratin-filled surface ostia

- Hand-lens inspection may reveal round, pore-like openings.
- Ostia are packed with keratin.
- These openings support epidermal keratinization as the source of the surface pattern.



Schematic: Keratin-filled surface pores
Original editable schematic; Not a clinical or histologic specimen

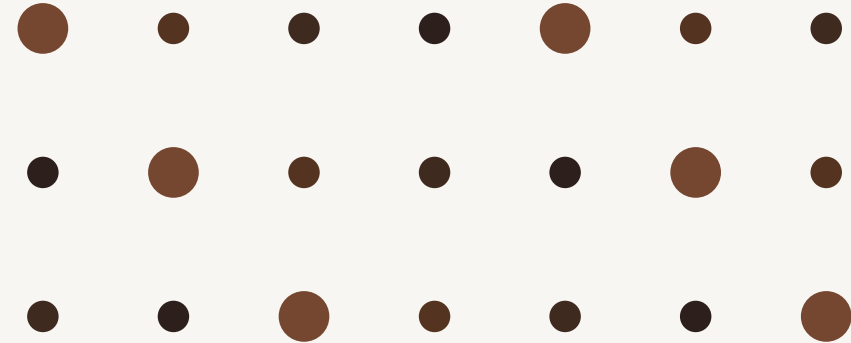
An integrated bedside description

A circumscribed, tan–brown, waxy plaque with a granular “stuck-on” surface and keratin-filled openings.

This combination is typical of seborrheic keratosis, but atypical lesions require further assessment.

Dermatosis papulosa nigra

- A recognized presentation related to seborrheic keratosis.
- Appears as multiple small, dark brown to black facial papules.
- Its occurrence in darker-skinned individuals.



Multiple small pigmented papules

Original editable schematic; Not a clinical or histologic specimen

Why dermatosis papulosa nigra matters

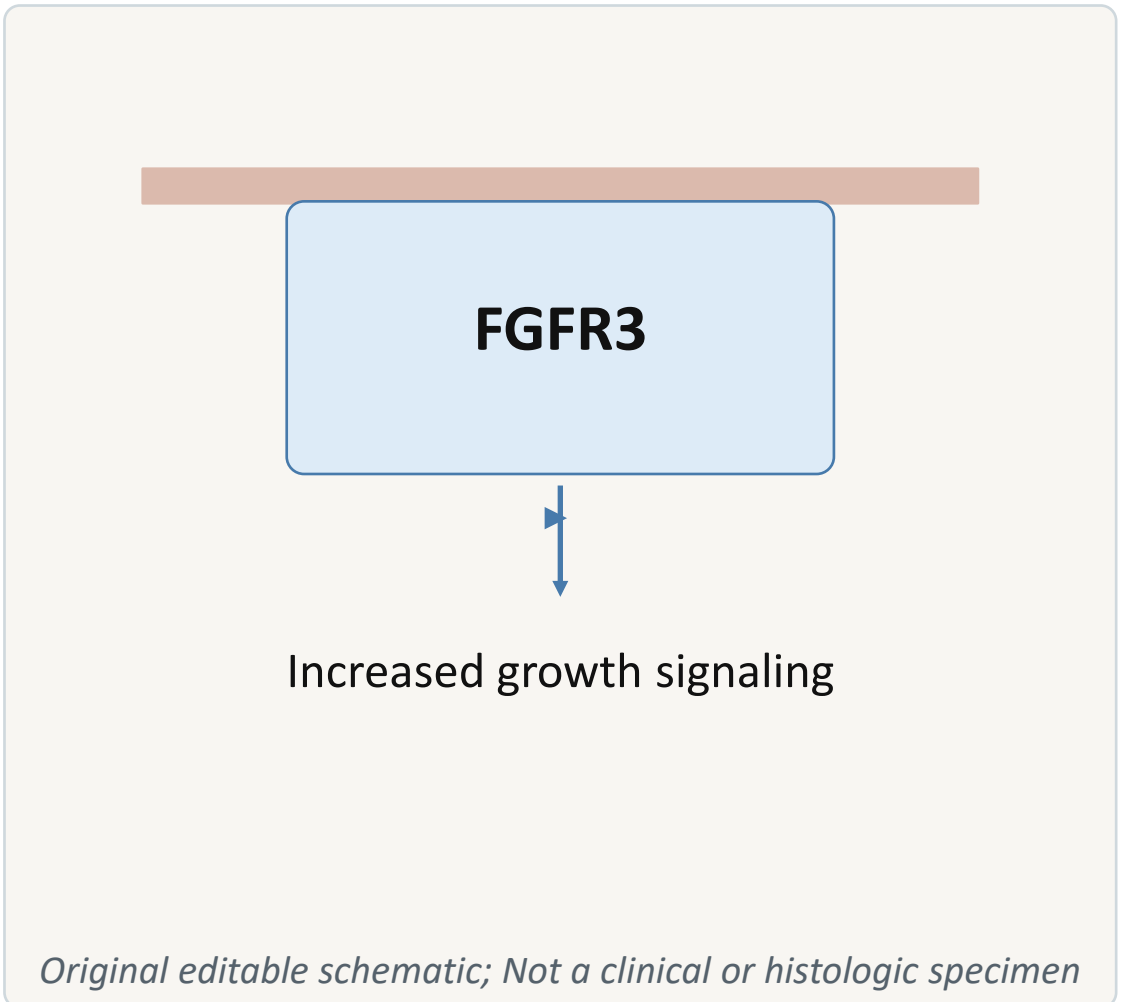
- Pigment intensity must be assessed relative to skin phototype.
- The combination of numerous small facial lesions forms a recognizable phenotype.
- Recognition prevents assuming that every dark facial papule is melanocytic.

Classical plaque versus DPN

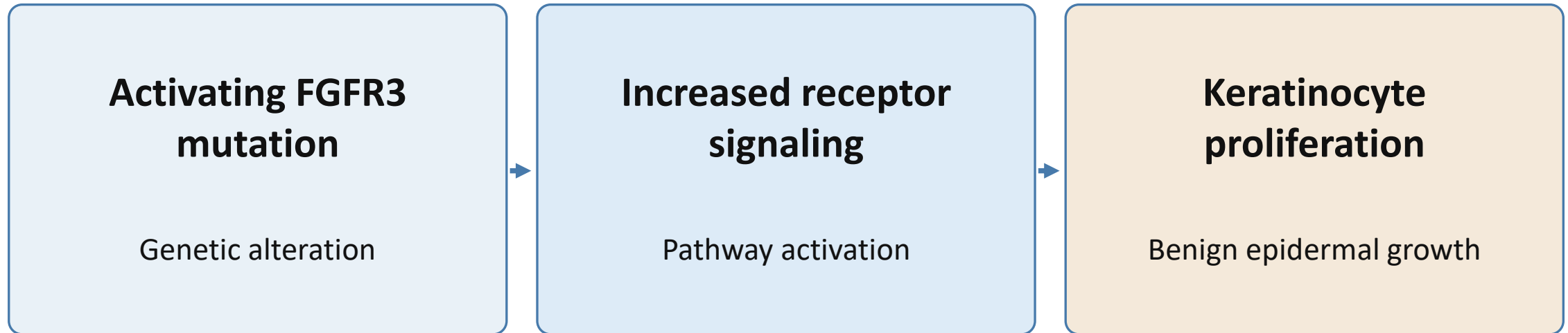
Typical seborrheic keratosis	Dermatosis papulosa nigra
Often trunk; other sites possible	Typically facial distribution
Tan to dark-brown waxy plaque	Small dark-brown to black papules
May be solitary or multiple	Often multiple
Shared benign epidermal lineage	Related clinicopathologic phenotype

FGFR3 is a receptor tyrosine kinase

- Fibroblast growth factor receptor 3 (FGFR3) is a surface signaling receptor.
- Activating FGFR3 mutations in many sporadic lesions.
- The mutation is implicated in lesion growth rather than used as a routine diagnostic requirement.



An activating mutation changes signaling



Causal schematic based on textbook statements; Molecular intermediates are not specified.

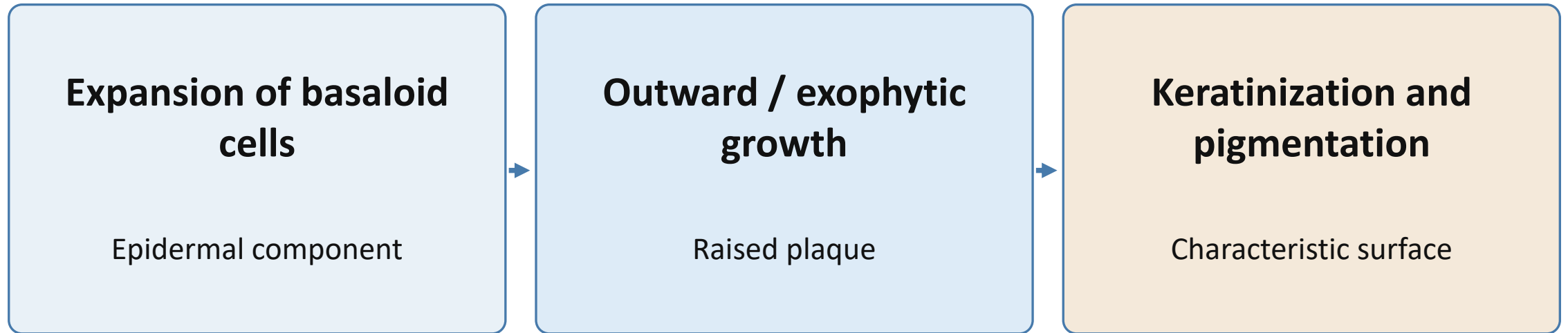
What FGFR3 does—and does not—show

Supported inference	Not established by FGFR3 alone
A growth-promoting driver in many SKs	A required mutation in every SK
A plausible mechanism of epidermal expansion	Malignant behavior
A molecular link with some acanthosis disorders	An indication for molecular testing in routine SK

Morphology is central to diagnosis

- The characteristic lesion is defined by architecture and differentiation.
- Histologic recognition does not depend on routine molecular analysis.
- Atypical pigmented lesions are evaluated by clinicopathologic correlation.

From an epidermal clone to a plaque

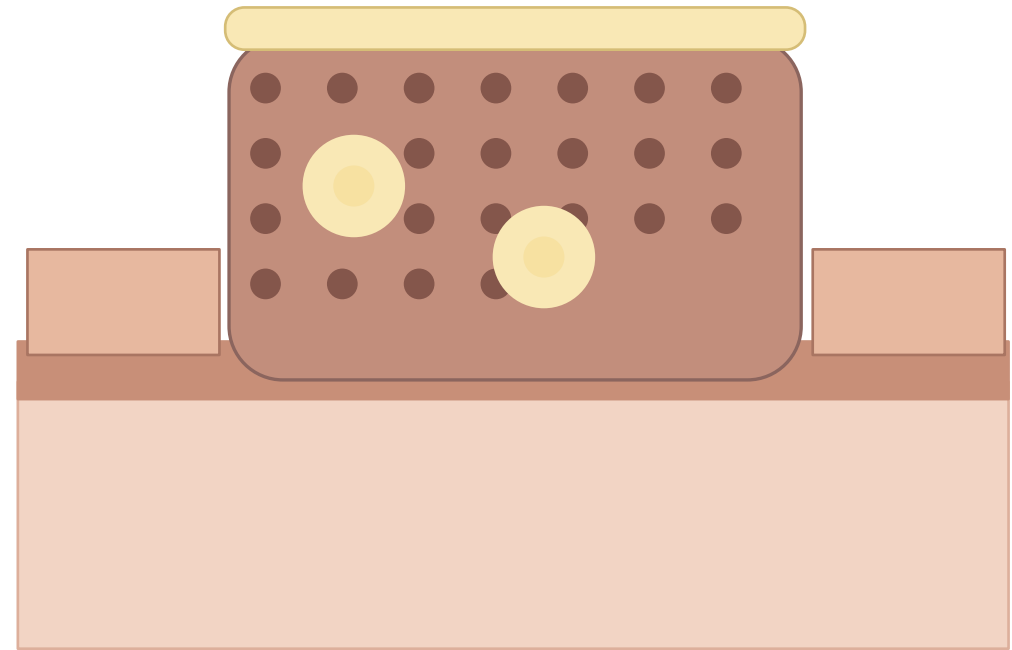


Causal schematic based on textbook statements; Molecular intermediates are not specified.

Exophytic growth: Directional concept

- The dominant growth is outward from the epidermal plane.
- The lesion projects above adjacent skin.
- Schematic represents architecture, not a diagnostic photomicrograph.

Exophytic projection

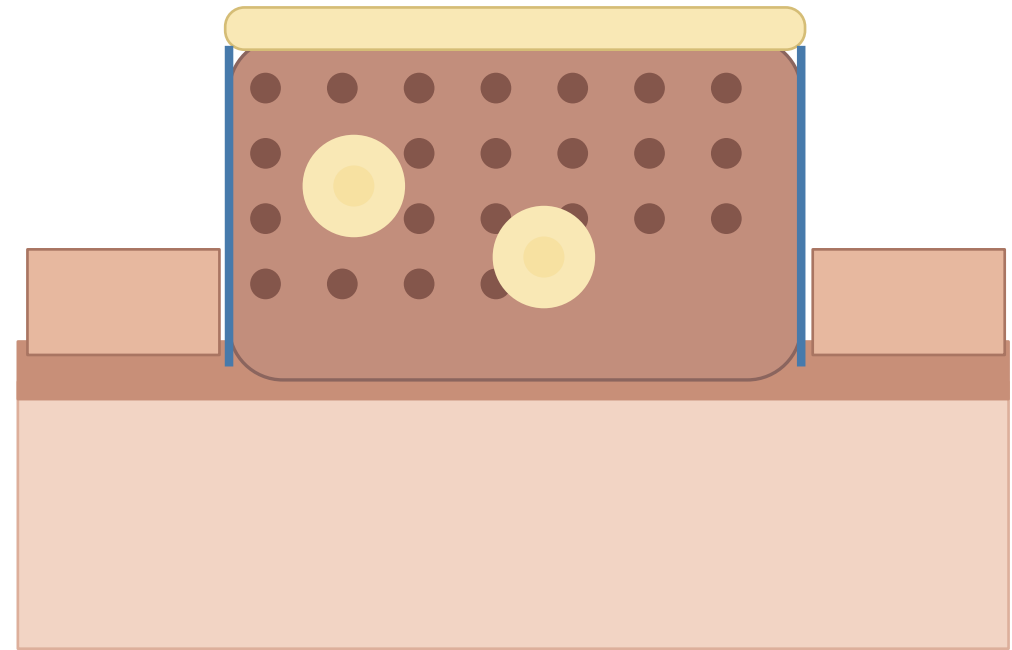


SCHEMATIC — not H&E

A sharply circumscribed interface

- Tumor is relatively well defined versus neighboring epidermis.
- Circumscription underlies the visible plaque-like border.
- Infiltrative/destructive growth should prompt reassessment.

Sharp lesion–epidermis interface

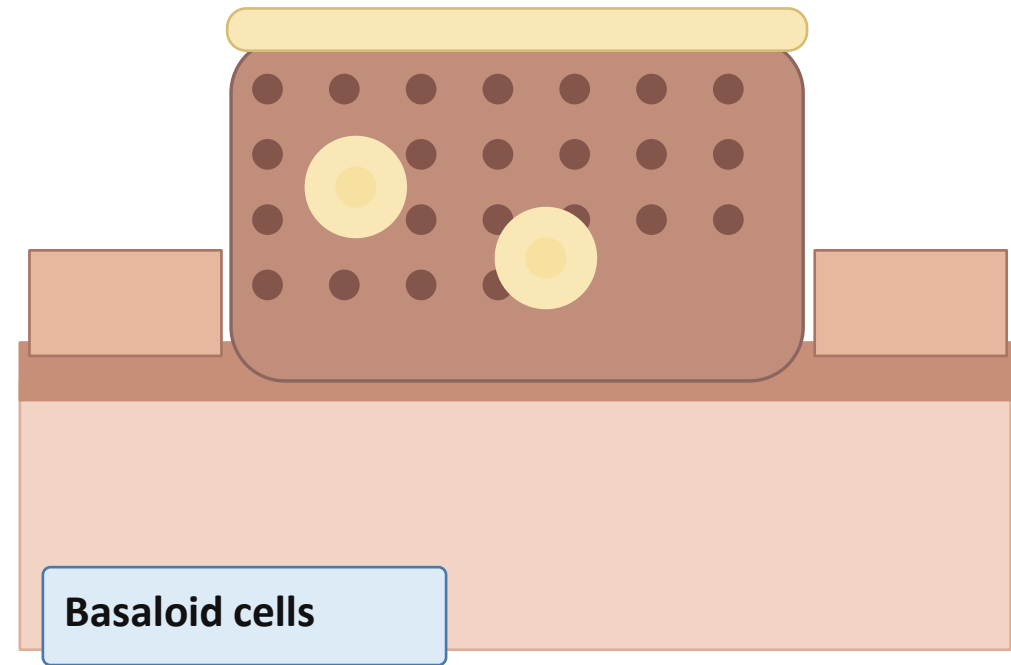


SCHEMATIC — not H&E

The basaloid epithelial population

- Sheets of small cells resemble basal epidermal keratinocytes.
- Uniform basaloid appearance is part of the classic phenotype.
- Interpret basaloid cytology within the overall epidermal architecture.

Basaloid epithelial expansion

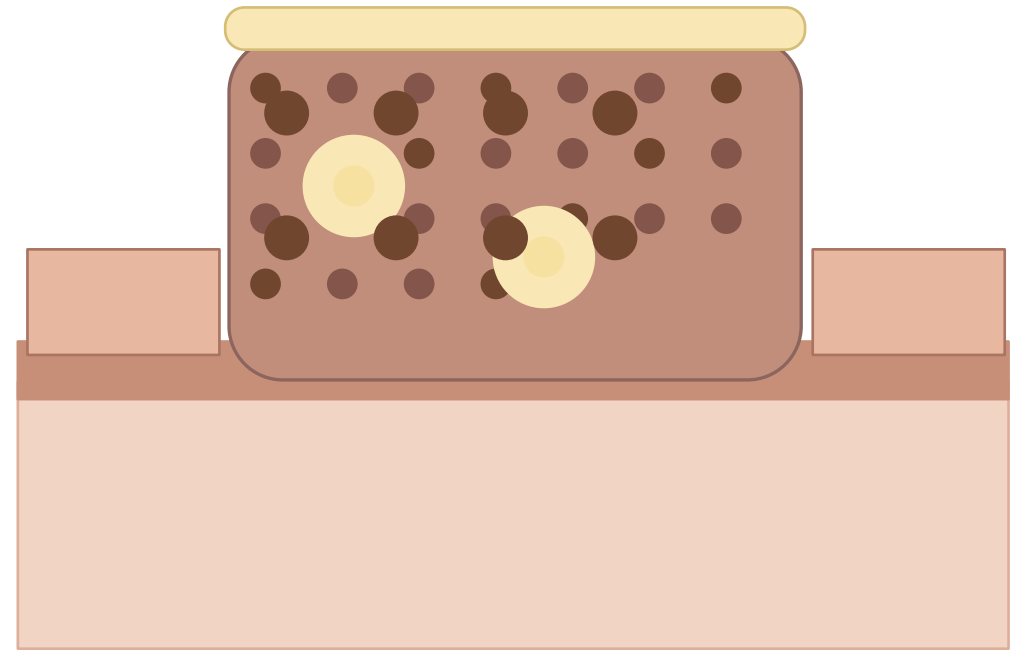


SCHEMATIC — not H&E

Pigmentation arises in basaloid cells

- Variable melanin occurs within the proliferating basaloid cells.
- This contributes to tan, brown or black coloration.
- Melanin does not convert the lesion into a melanocytic neoplasm.

Melanin in basaloid cells

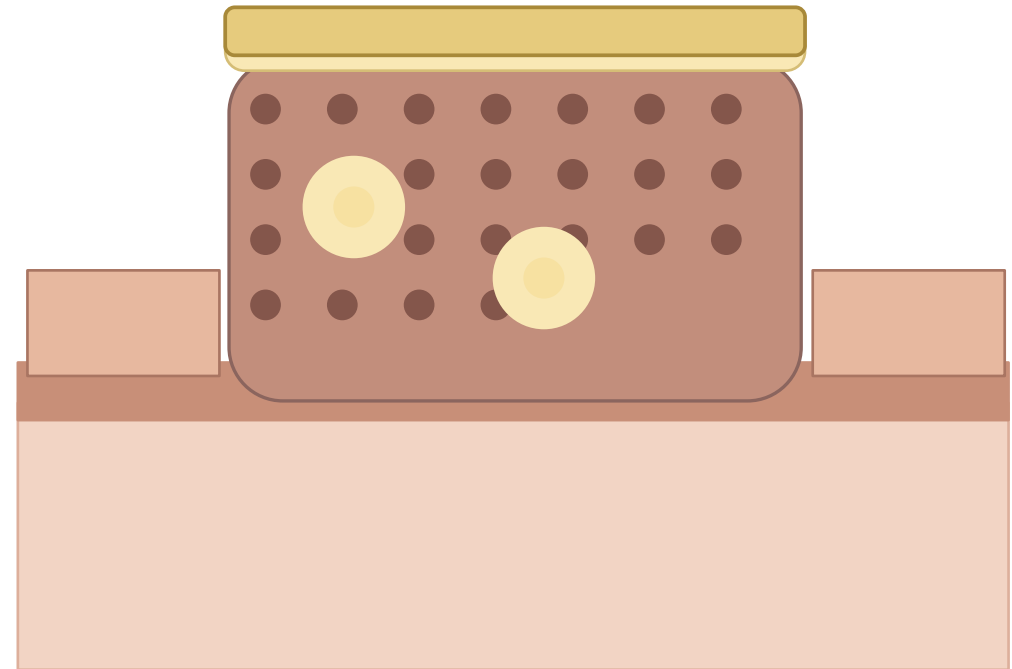


SCHEMATIC — not H&E

Hyperkeratosis at the surface

- A thickened keratin layer overlies the epidermal growth.
- Surface keratin contributes to a rough, waxy or granular appearance.
- Keratin may also accumulate within epithelial pockets.

Surface hyperkeratosis

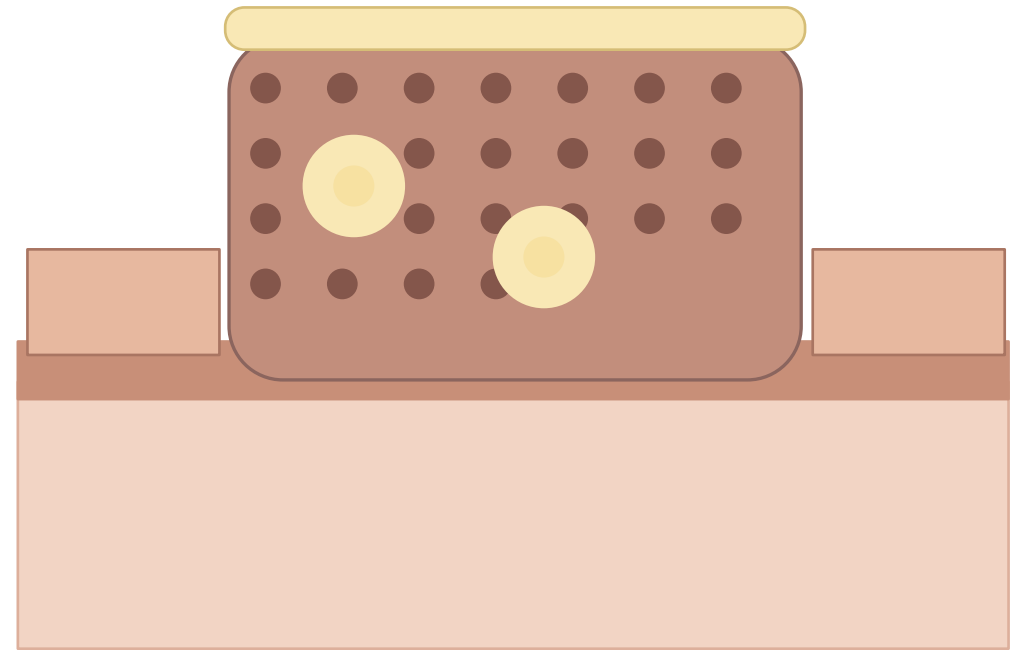


SCHEMATIC — not H&E

Horn cysts are keratin-filled spaces

- Intraepidermal round spaces are packed with keratin.
- They are characteristic of the lesion.
- The lining is part of the epidermal epithelial proliferation.

Intraepidermal horn cysts

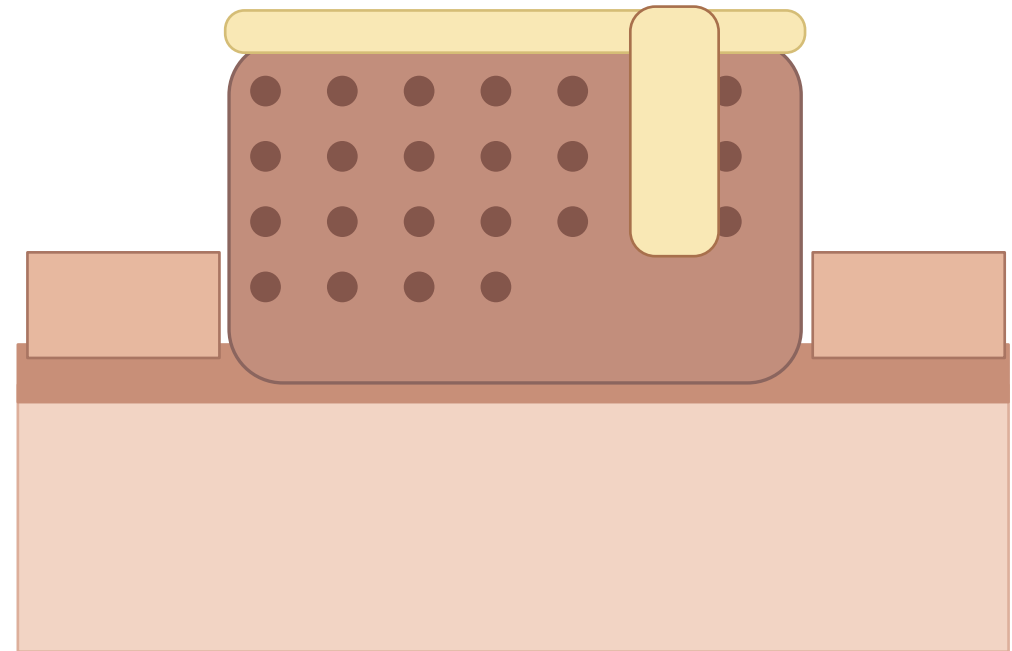


SCHEMATIC — not H&E

Invagination cysts communicate with the surface

- Surface epidermis may fold inward into the tumor.
- Keratin accumulates in the invaginated space.
- On section these appear as pseudohorn / invagination cysts.

Surface-connected invagination



SCHEMATIC — not H&E

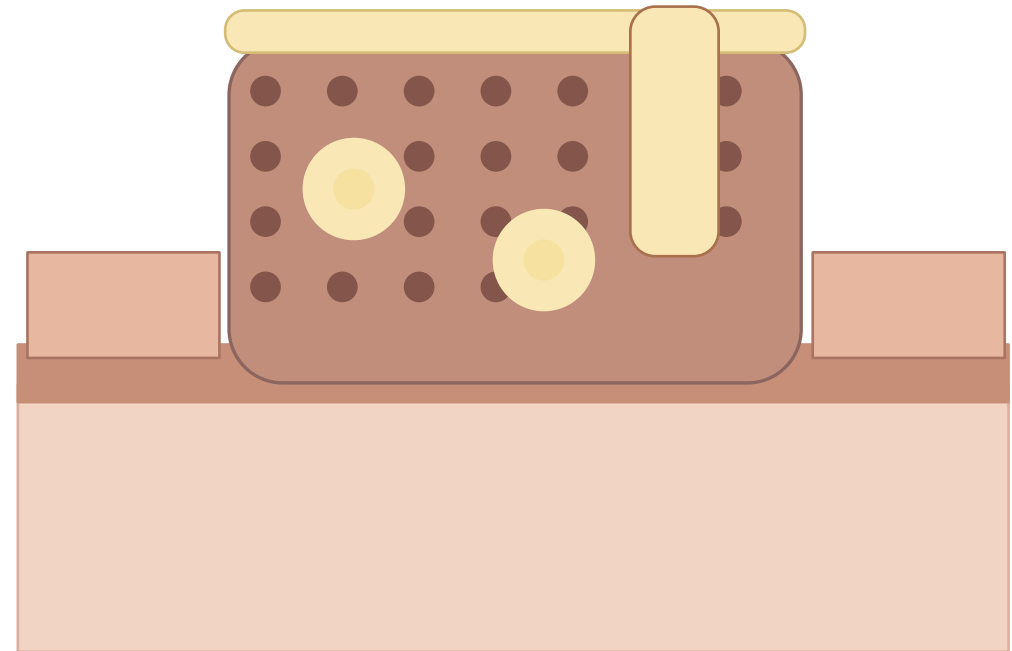
Horn cyst versus pseudohorn cyst

True horn cyst	Pseudohorn / invagination cyst
Closed keratin-containing intraepidermal space	Keratin-containing invagination
No direct surface continuity in the section	Connection to surface may be demonstrable
May correspond to white-yellow dermoscopic dots	May correspond to dark comedo-like openings

Where the horn structures form

- Horn cysts lie within basaloid epidermal proliferation.
- Pseudohorn cysts are surface-connected invaginations.
- Distribution and size vary across a lesion.

Two keratin-filled architectures

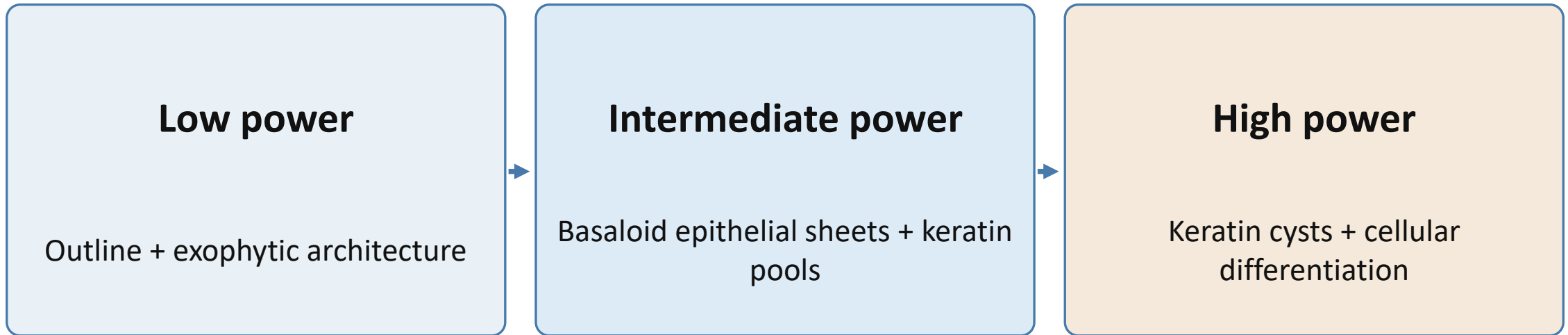


SCHEMATIC — not H&E

A low-power histologic checklist

- Exophytic and sharply demarcated epidermal proliferation.
- Small basaloid cells within the expanded epidermis.
- Surface hyperkeratosis.
- Keratin-filled horn cysts and surface invaginations.
- Variable melanin pigmentation.

From low power to high power



Causal schematic based on textbook statements; Molecular intermediates are not specified.

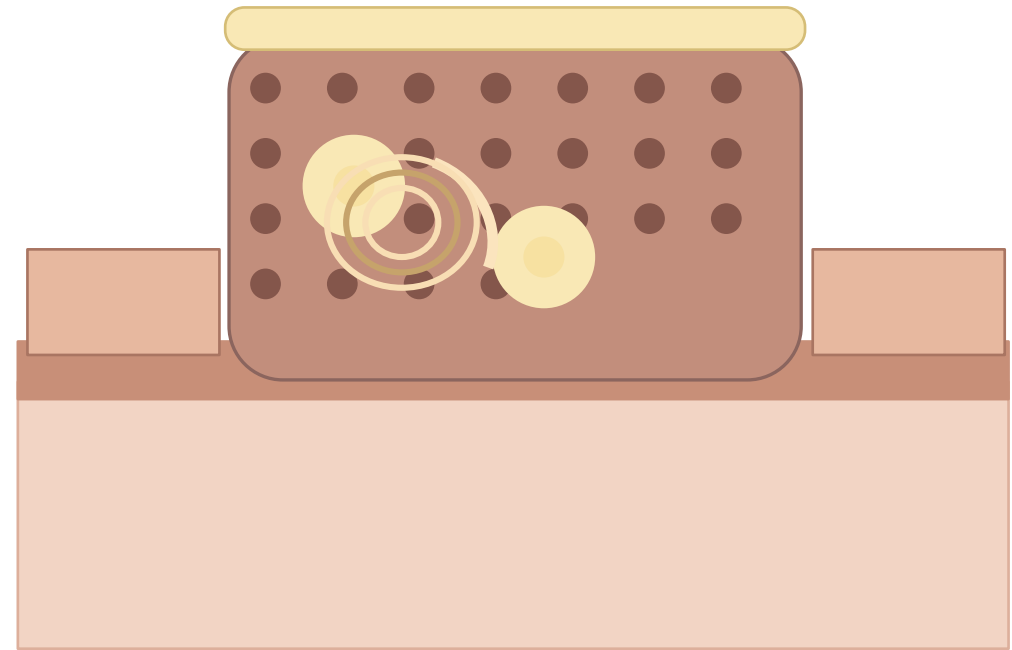
Irritation changes the histologic picture

- An irritated lesion may become inflamed.
- Reactive squamous differentiation can become more prominent.
- Interpret changes alongside residual classic seborrheic keratosis architecture.

Squamous eddies in irritated lesions

- Whirling foci of squamous differentiation can develop.
- The pattern to eddy currents.
- Squamous eddies should not be equated automatically with invasion.

Squamous eddy pattern



SCHEMATIC — not H&E

Inflammation can obscure recognition

- Clinical erythema or irritation may alter the usual waxy appearance.
- Histologic squamous maturation may dominate a portion of the section.
- Sampling and morphology determine whether an alternative diagnosis must be excluded.

**Atypical pattern ≠
Benign diagnosis**

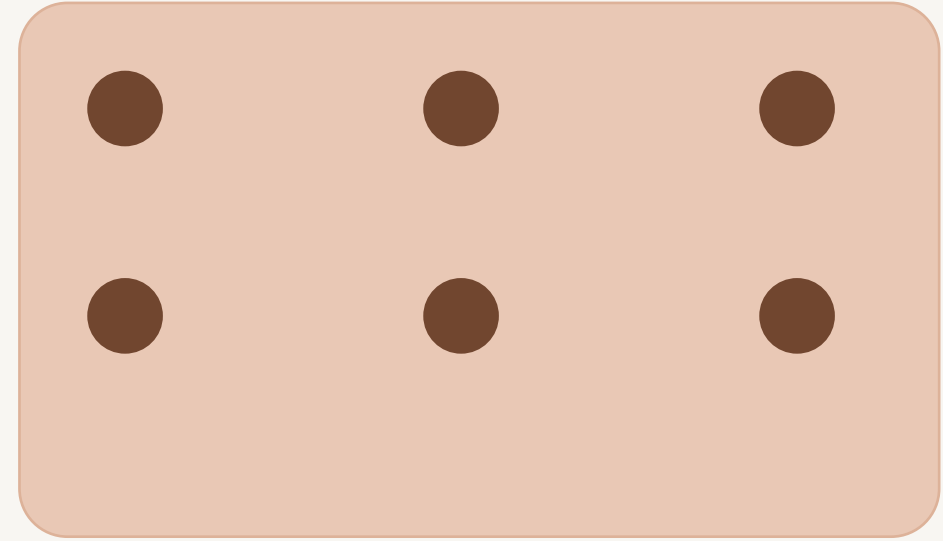
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Clinical finding and histologic counterpart

Clinical / dermoscopic observation	Principal morphologic correlate
Stuck-on, raised border	Exophytic sharply demarcated lesion
Waxy, granular surface	Hyperkeratosis and surface relief
Brown to black pigmentation	Melanin in basaloid cells
Keratin plugs / openings	Invagination / pseudohorn cysts
White–yellow cyst-like structures	Intraepidermal keratin-filled cysts

Dermoscopy: Comedo-like openings

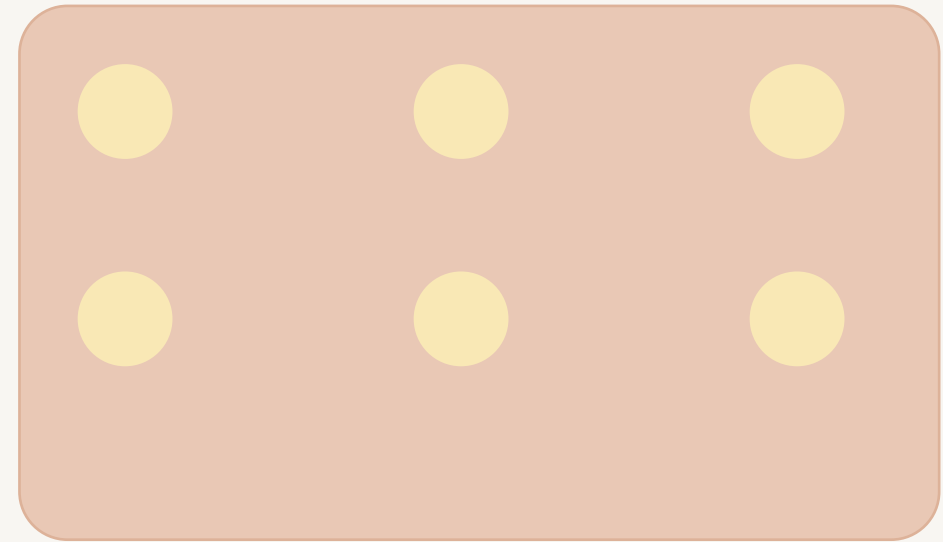
- Dark round or irregular crypts are common clues.
- These correlate with keratin-filled surface connections.
- They are supportive, not pathognomonic.



Schematic: Keratin-filled surface pores
Original editable schematic; Not a clinical or histologic specimen

Dermoscopy: Milia-like cysts

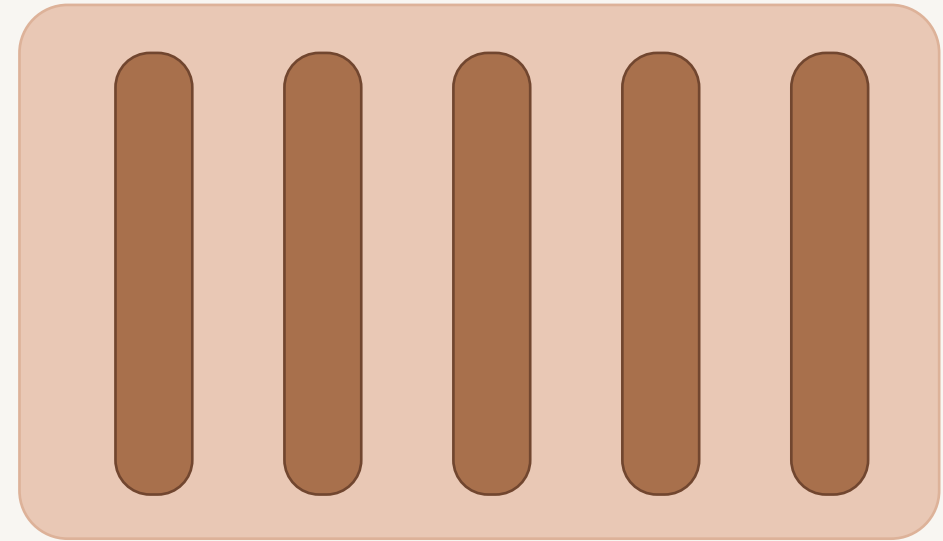
- White or yellow clods may reflect intraepidermal keratin.
- Histologic horn cysts explain this appearance.
- The finding alone cannot exclude melanoma or other tumors.



Schematic: Keratin-filled intraepidermal spaces
Original editable schematic; Not a clinical or histologic specimen

Dermoscopy: Fissures and ridges

- Fissures separate raised ridges of the epidermal surface.
- A cerebriform pattern may result.
- These observations complement the clinical stuck-on appearance.



Schematic: Fissures alternating with ridges
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Why dermoscopic clues are not absolute

- Seborrheic keratosis can show asymmetry and multiple colors.
- Melanoma and basal cell carcinoma occasionally share isolated SK-like structures.
- Discordant evolution or atypical findings warrant definitive evaluation.

Differential: Pigmented melanoma

Favored seborrheic keratosis	Findings that require melanoma assessment
Waxy, surface-keratin pattern	Changing shape, color or size
Well-defined exophytic lesion	Irregular contour and variegated pigmentation
Horn / pseudohorn cyst morphology	Melanocytic atypia or malignant architecture on histology

Differential: Actinic keratosis

Seborrheic keratosis	Actinic keratosis
Common waxy plaque; variable sites	Rough sandpaper lesion at sun-exposed sites
Basaloid cells and horn cysts	Basal keratinocyte cytologic atypia
Benign epidermal neoplasm	May progress toward squamous cell carcinoma

Differential: Pigmented basal cell carcinoma

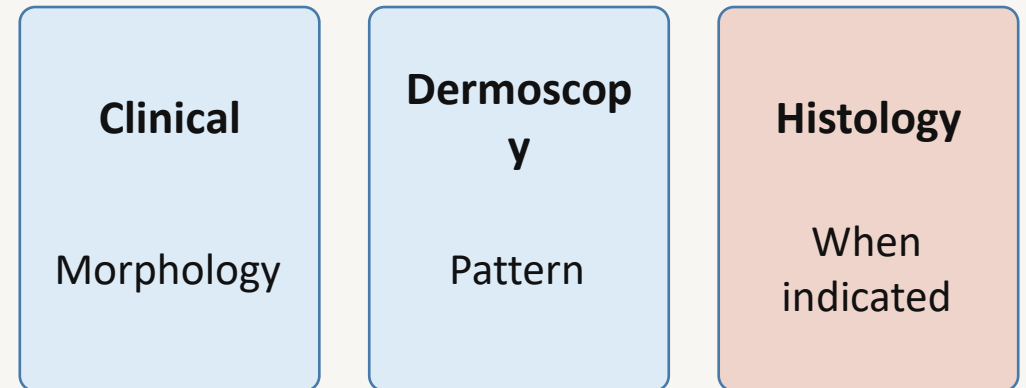
Seborrheic keratosis	Basal cell carcinoma
Surface-based, keratinizing basaloid proliferation	Locally invasive carcinoma
Keratin-filled cysts favor SK	Dermal tumor nests with characteristic BCC architecture
No characteristic invasive growth	Hedgehog signaling pathway is implicated

Differential: Acanthosis nigricans

Seborrheic keratosis	Acanthosis nigricans
Discrete plaques / papules	Diffuse velvety thickening, especially flexures
Horn cysts and basaloid growth	Undulating epidermis + enlarged dermal papillae
May be sporadic with FGFR3 mutation	Often associated with metabolic/endocrine disorders

A practical differential framework

- Ask first whether the lesion is an epidermal plaque, a melanocytic lesion, or invasive tumor.
- Seek supporting keratinization features without over-relying on them.
- Use histology when the clinical–dermoscopic pattern is atypical.



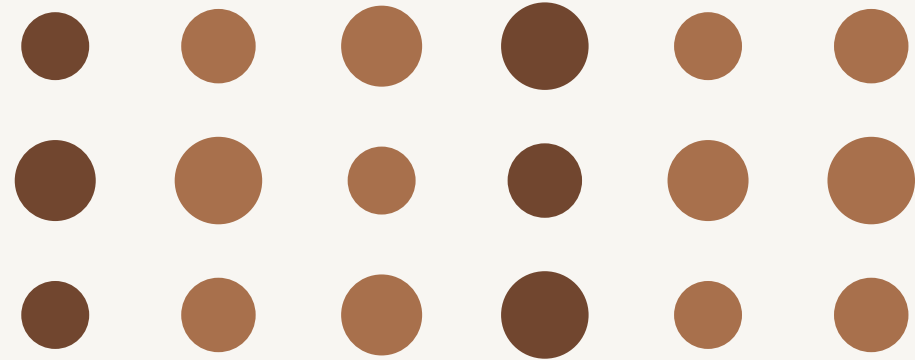
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When histologic assessment becomes important

- Unusual pigmentation, shape or surface morphology.
- Changes that are not typical of established benign lesions.
- Concern for melanoma, basal cell carcinoma or squamous neoplasia.
- Clinical findings inconsistent with a straightforward diagnosis.

Leser–Trélat: Abrupt eruption of lesions

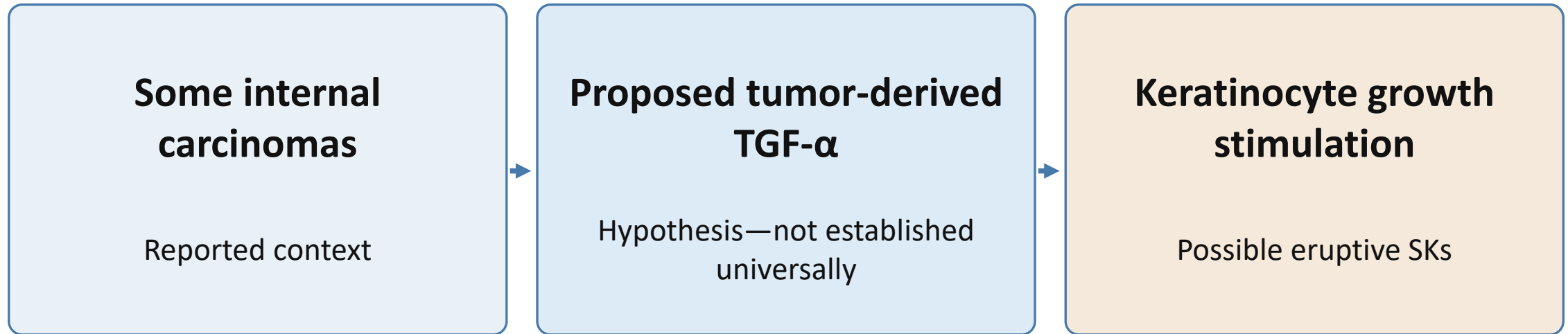
- A sudden appearance of numerous seborrheic keratoses has been described as the Leser–Trélat sign.
- An association with internal malignancy.
- The historical paraneoplastic interpretation remains debated.



Conceptual: Abrupt multiplicity

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Proposed growth-factor mechanism



Proposed mechanism: The TGF-α link is hypothetical, not universal.

The cancer association is not deterministic

- Gastrointestinal carcinomas among associated tumors.
- Seborrheic keratoses are independently common in older adults.
- Coincidence and selection bias complicate causal interpretation.
- An abrupt eruption is a clinical cue, not a cancer diagnosis.

Leser–Trélat and diagnostic restraint

- Obtain a careful history and examination when lesions erupt abruptly.
- Assess accompanying systemic or cutaneous findings in context.
- Avoid representing TGF- α mediation as proven for all cases.

**Atypical pattern $\neq$
Benign diagnosis**

Original editable schematic; Not a clinical or histologic specimen

Acanthosis nigricans in the same context

- Presents as thickened, hyperpigmented, velvety flexural skin.
- Many cases associate with obesity, insulin resistance or endocrine causes.
- A minority occur as a paraneoplastic phenomenon.

**Flexural skin:
Neck, axillae, groin**

Original editable schematic; Not a clinical or histologic specimen

Histology of acanthosis nigricans

Acanthosis nigricans	Seborrheic keratosis
Papillary undulation forming peaks and valleys	Exophytic sharply defined epidermal tumor
Hyperkeratosis ± epidermal hyperplasia	Basaloid expansion + horn cysts
Basal pigmentation without melanocytic hyperplasia	Variable melanin in basaloid cells

A shared receptor does not mean one disease

- FGFR3 activation is described in many sporadic seborrheic keratoses.
- Familial acanthosis nigricans may involve germline FGFR3 mutations.
- Differing phenotypes are not fully explained.
- Tissue architecture and clinical setting remain essential.

Case 1: A waxy trunk plaque

Constructed teaching vignette

A 68-year-old has a long-standing oval, sharply bordered brown plaque on the back. The surface appears waxy, granular and “stuck on.”

Diagnostic question

Which clinical features most favor seborrheic keratosis?

Interpretation

Combination of well-defined raised plaque, waxy/granular surface and keratin-related surface openings; Inspect for atypical features.

Case 2: The epidermal biopsy pattern

Constructed teaching vignette

Biopsy shows an exophytic circumscribed proliferation of small basaloid epithelial cells, hyperkeratosis, and multiple keratin-filled cysts.

Diagnostic question

Which structures carry the most diagnostic weight?

Interpretation

Horn cysts and surface-connected keratin invaginations within a characteristic basaloid, exophytic proliferation.

Case 3: Numerous dark facial papules

Constructed teaching vignette

An older adult with deeply pigmented skin has many small dark-brown to black facial papules of similar morphology.

Diagnostic question

Which seborrheic keratosis phenotype should be considered?

Interpretation

Dermatosis papulosa nigra. Evaluate lesions that differ from the common pattern on their own merits.

Case 4: A change that breaks the pattern

Constructed teaching vignette

A patient with several stable waxy plaques develops one lesion with a distinctly changing outline and heterogeneous pigmentation.

Diagnostic question

Should the new lesion be assumed to be another seborrheic keratosis?

Interpretation

No. Pigmented malignancy remains a differential; Clinical examination, dermoscopy and biopsy when indicated are appropriate.

Case 5: Sudden widespread eruption

Constructed teaching vignette

A patient reports rapid appearance of many clinically similar keratoses over a short interval.

Diagnostic question

How should the potential Leser–Trélat association be communicated?

Interpretation

An eruptive pattern has been reported with internal tumors, but the causal association is debated; Clinical context guides evaluation.

Synthesis: Diagnostic reasoning

SK is a benign epidermal tumor whose macroscopic “stuck-on” morphology mirrors an exophytic basaloid proliferation with surface keratinization and horn cysts.

Recognize classic morphology, but do not use one benign feature to dismiss an atypical lesion.

References and image policy

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 25, pp. 1036–1037 and adjacent skin-lesion sections.
- DermNet. Dermoscopy of seborrhoeic keratosis; Sign of Leser–Trélat.
- Minagawa A. Dermoscopy–pathology relationship in seborrheic keratosis. J Dermatol. 2017;44:518–524. doi:10.1111/1346-8138.13657
- All histologic/clinical-looking drawings in this lecture are original editable schematics—not patient photographs or tissue micrographs.