

Extramammary Paget Disease

Vulvar pathology: clinical appearance, morphology, diagnosis and biologic behavior

Dr Abu Suraih Sakhri

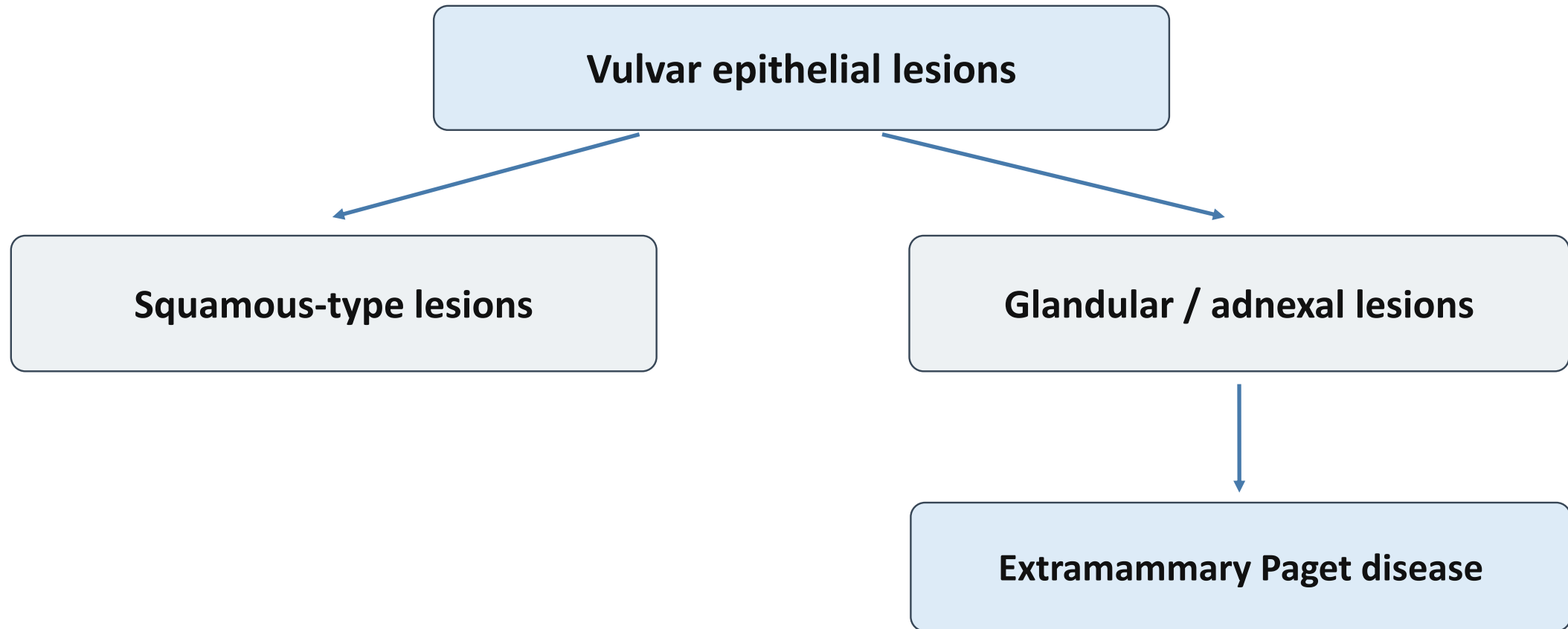
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Recognize the clinical and microscopic pattern of vulvar Paget disease.
- Explain the utility of mucin stains and CK7 in its evaluation.
- Differentiate intraepidermal disease from invasive disease and major mimics.
- Relate lateral epidermal spread to excision and long-term behavior.

Vulvar epithelial tumors: Orient the differential



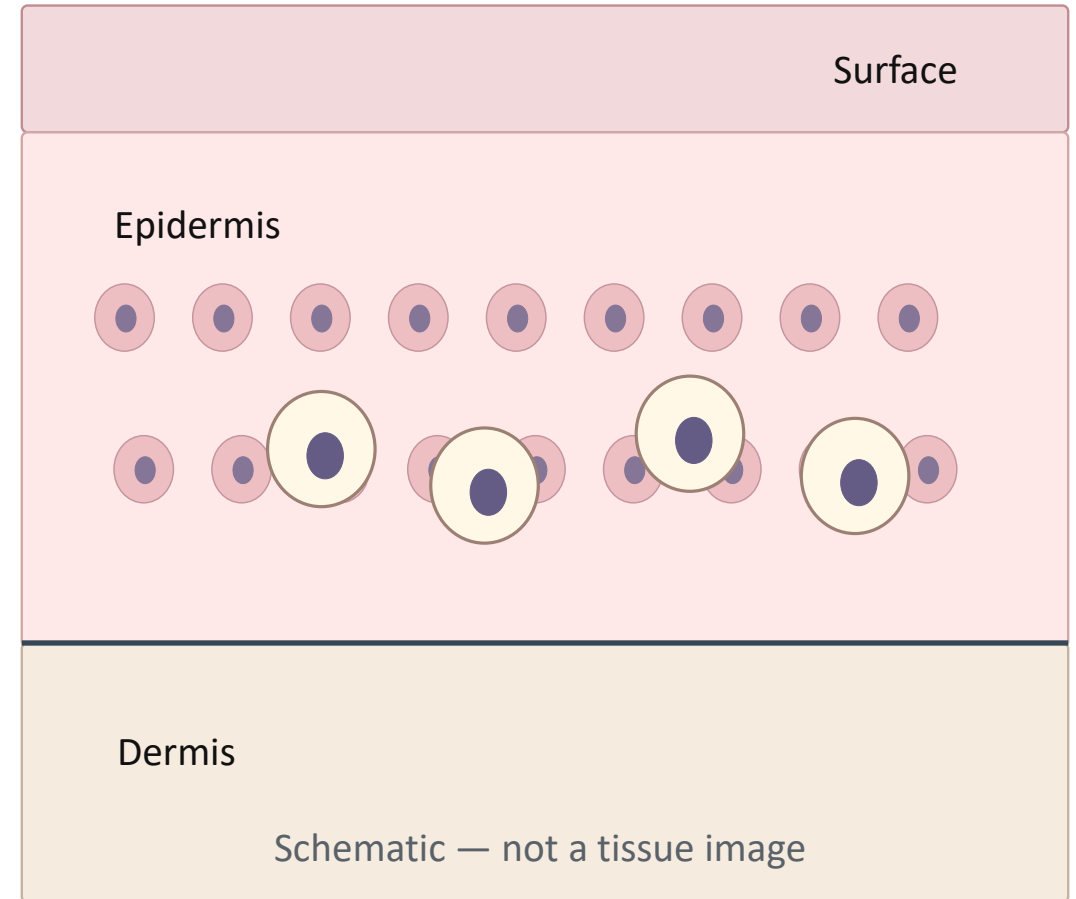
Two distinct differentiation patterns; Paget disease belongs in the glandular-type differential.

The vulva contains modified apocrine glands

- The vulva contains modified apocrine-type structures with breastlike features.
- This anatomic context helps explain glandular-type vulvar tumors.
- Robbins groups Paget disease with other vulvar glandular lesions.

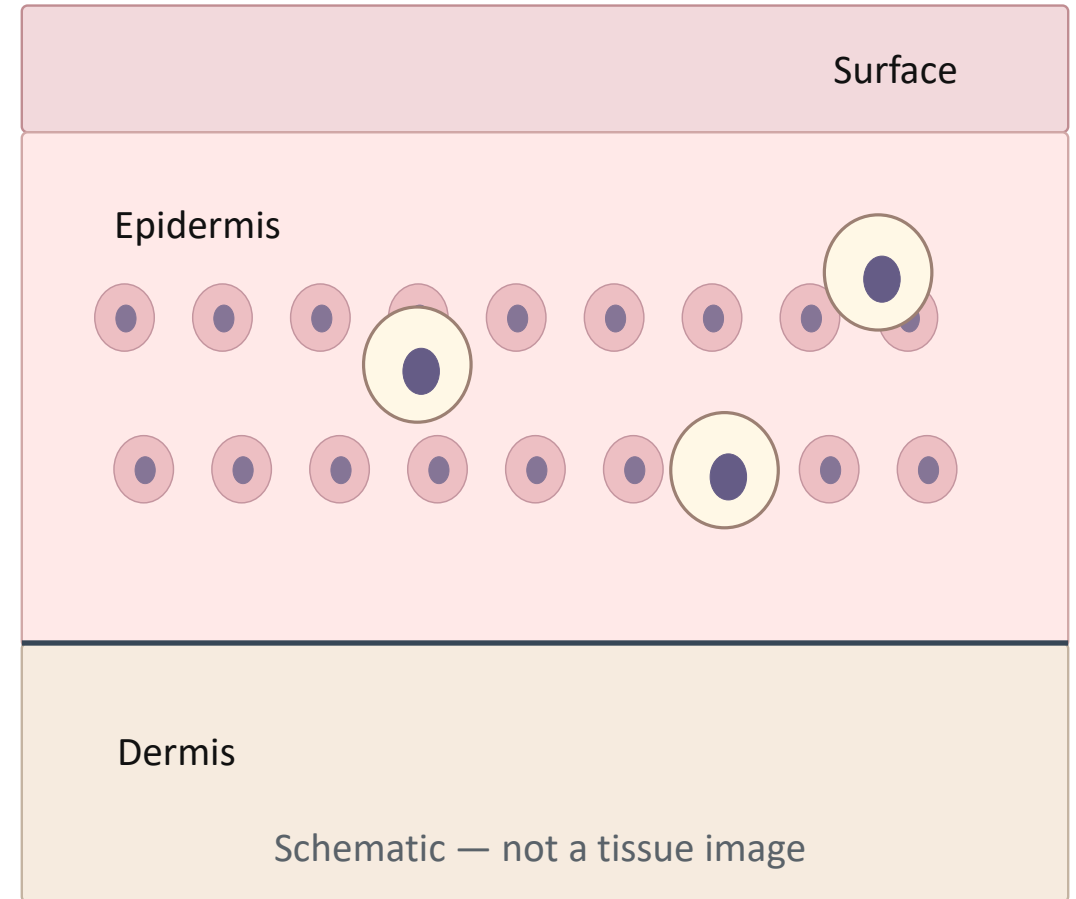
Definition: Malignant cells within epidermis

- Paget disease is a distinctive intraepithelial proliferation of malignant cells.
- The malignant glandular-type cells occupy otherwise squamous epidermis.
- An intraepidermal location does not itself establish dermal invasion.



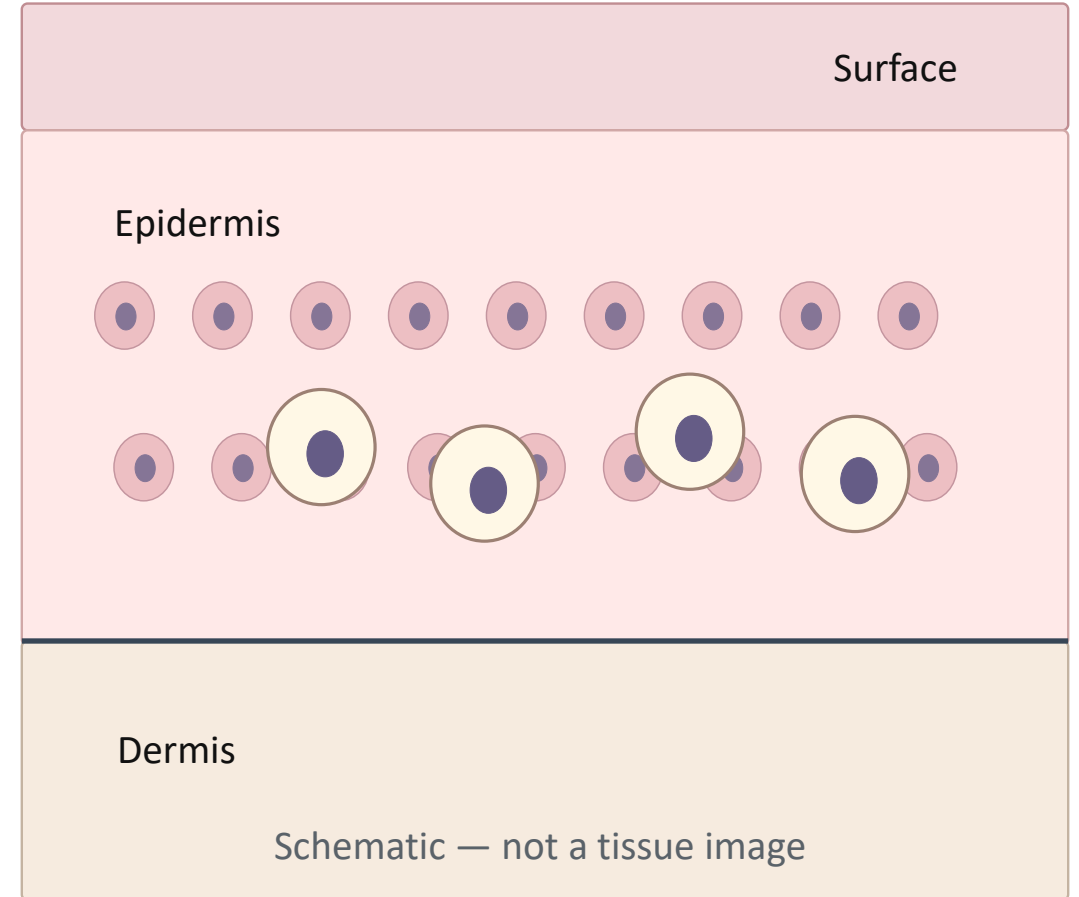
The Paget cell is not an ordinary keratinocyte

- Affected cells differ from surrounding squamous keratinocytes.
- They appear large, with pale mucin-containing cytoplasm.
- These differences create the recognizable histologic pattern.



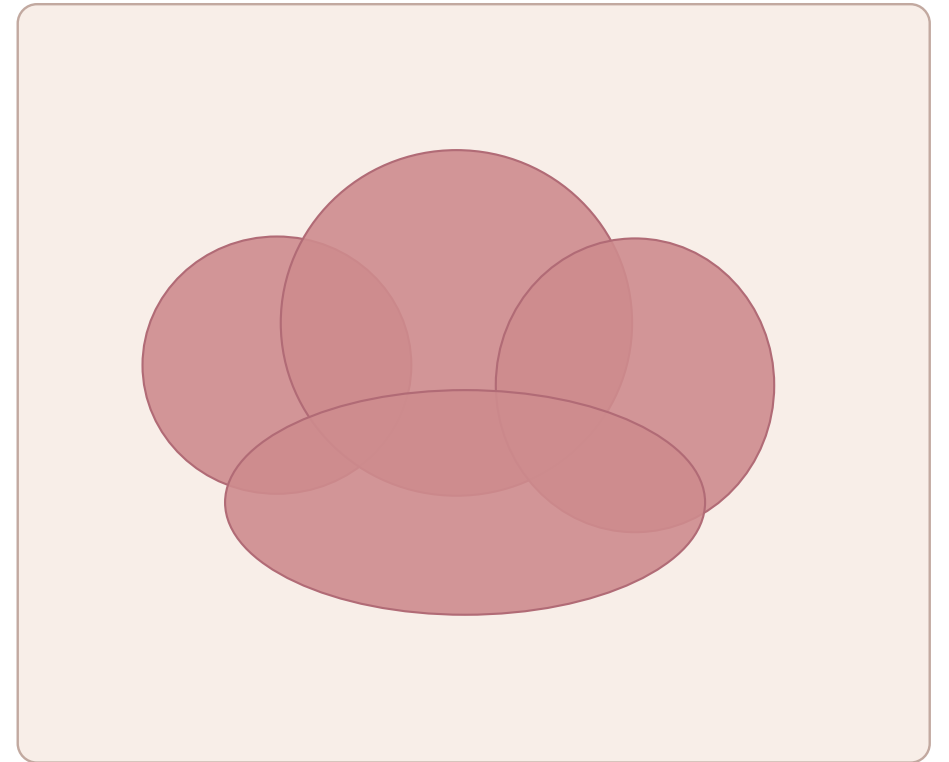
Intraepithelial disease is an anatomic designation

- Intraepithelial: Malignant cells remain above the basement membrane.
- Invasive: Malignant cells extend into underlying stroma.
- This distinction is biologically and prognostically important.



The labia majora are a typical clinical site

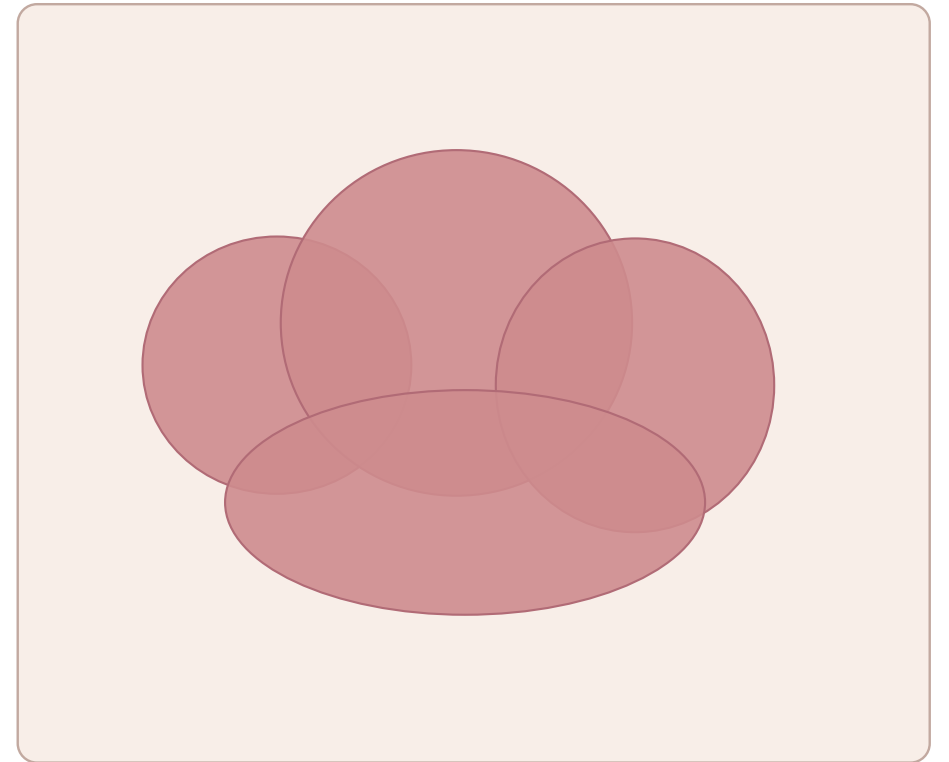
- Vulvar Paget disease often presents on the labia majora.
- The lesion is primarily a superficial skin abnormality.
- Site and appearance guide biopsy but cannot replace histology.



Pruritic erythematous plaque (schematic)

A characteristic clinical triad

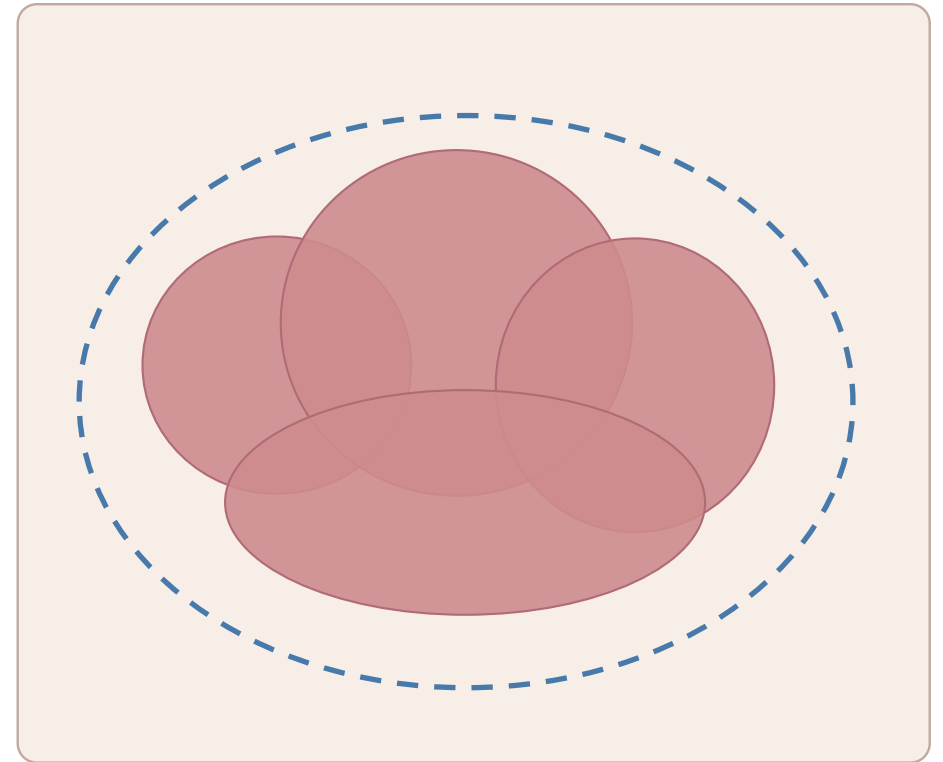
- Pruritus is a prominent symptom.
- The lesion is erythematous and crusted.
- A maplike, irregular plaque is a classic description.



Pruritic erythematous plaque (schematic)

Why the gross contour can mislead

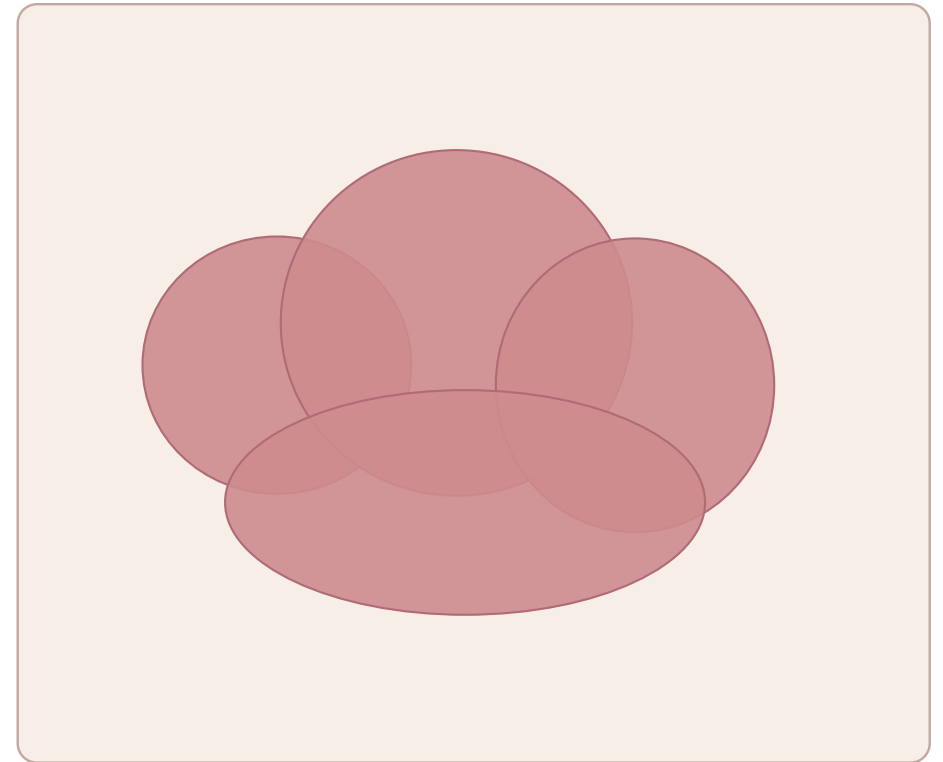
- A visible red plaque shows the clinically apparent component.
- Paget cells may extend laterally beyond its visible perimeter.
- Gross boundaries and microscopic boundaries are not equivalent.



Dashed outline: Conceptual microscopic extent

The clinical differential begins with dermatitis

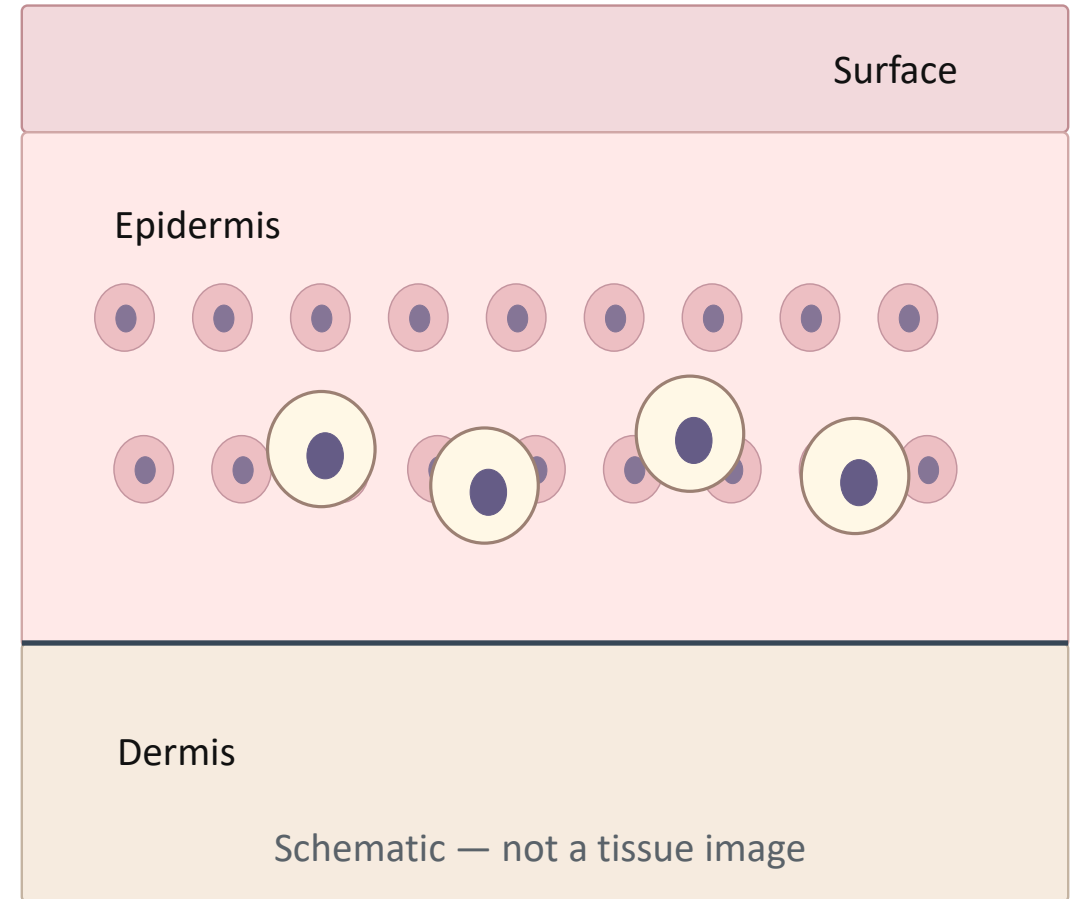
- An eczematous vulvar patch is not specific for neoplasia.
- Inflammatory skin conditions can resemble its surface appearance.
- Persistent or atypical lesions require histologic assessment.



Pruritic erythematous plaque (schematic)

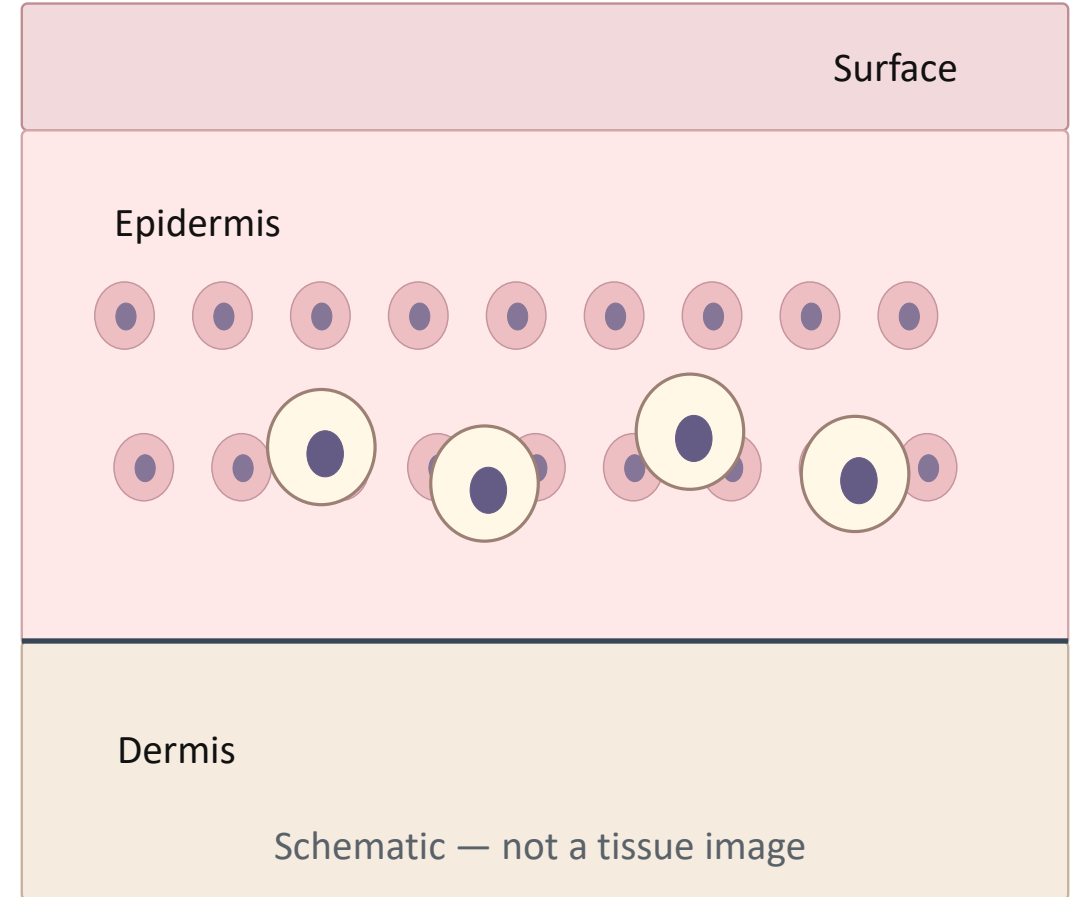
Clinical appearance cannot demonstrate invasion

- Color, itch and crusting reflect surface pathology.
- Invasion requires evaluation of the epidermal–dermal interface.
- A biopsy provides the tissue architecture needed for assessment.



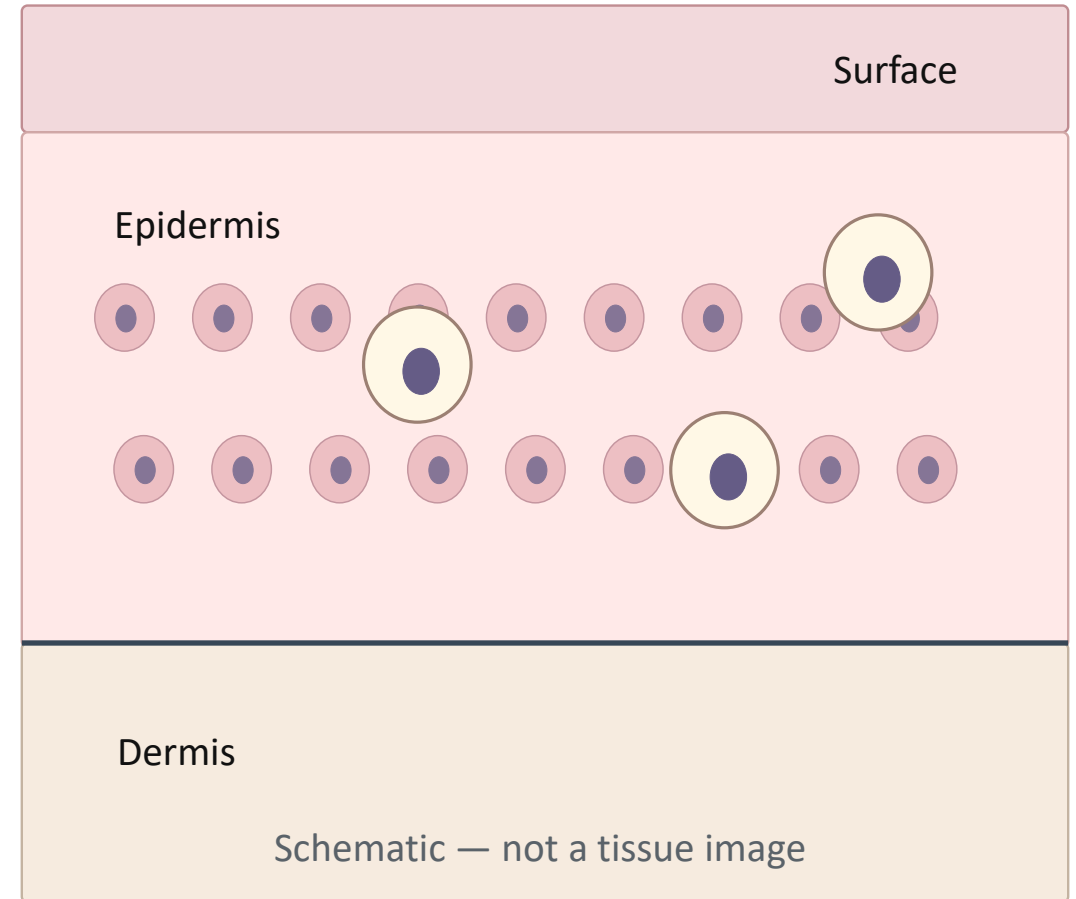
Low-power H&E: Scan the epidermis

- First identify the surface epidermis and underlying dermis.
- Look for pale enlarged cells scattered within squamous epithelium.
- Preserve the orientation of the dermoepidermal junction.



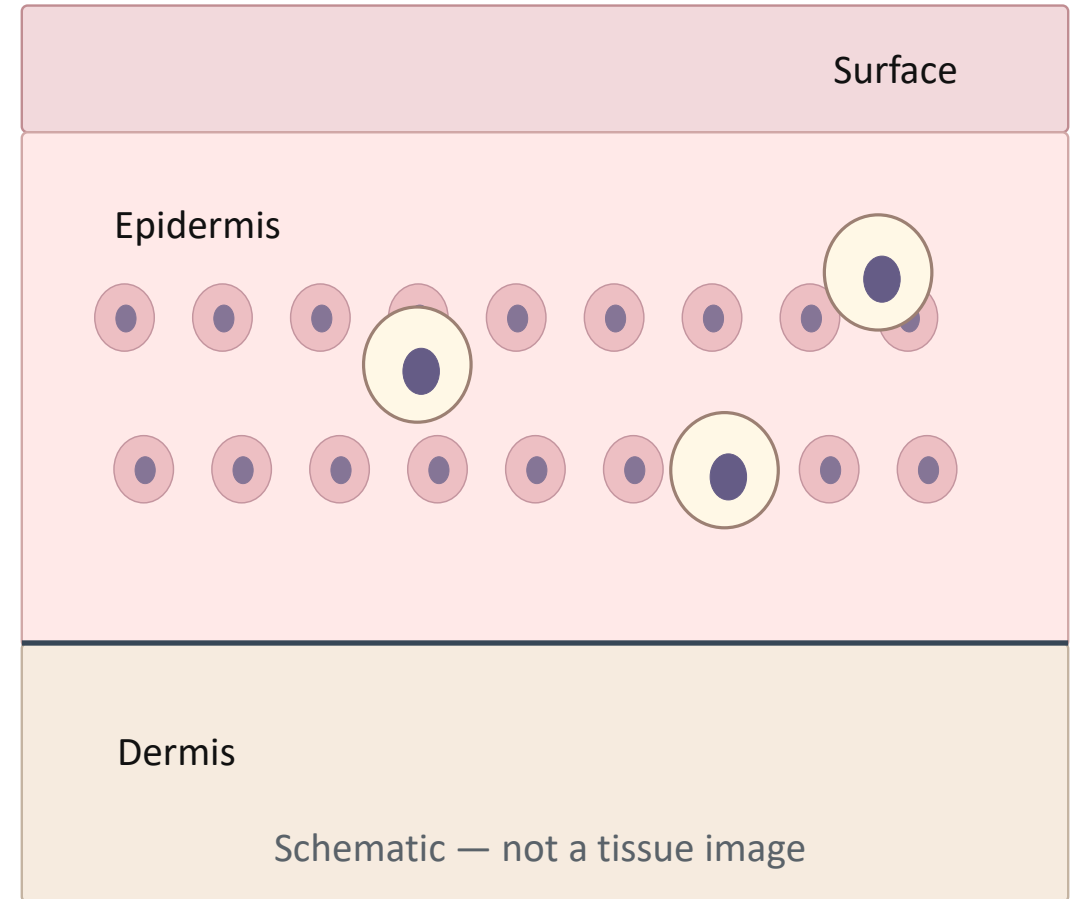
The basal epidermis is an important search zone

- Paget cells may be concentrated in the lower epidermis.
- Scattered pale cells are easier to miss near the basal region.
- Review the lower epidermis deliberately at scanning magnification.



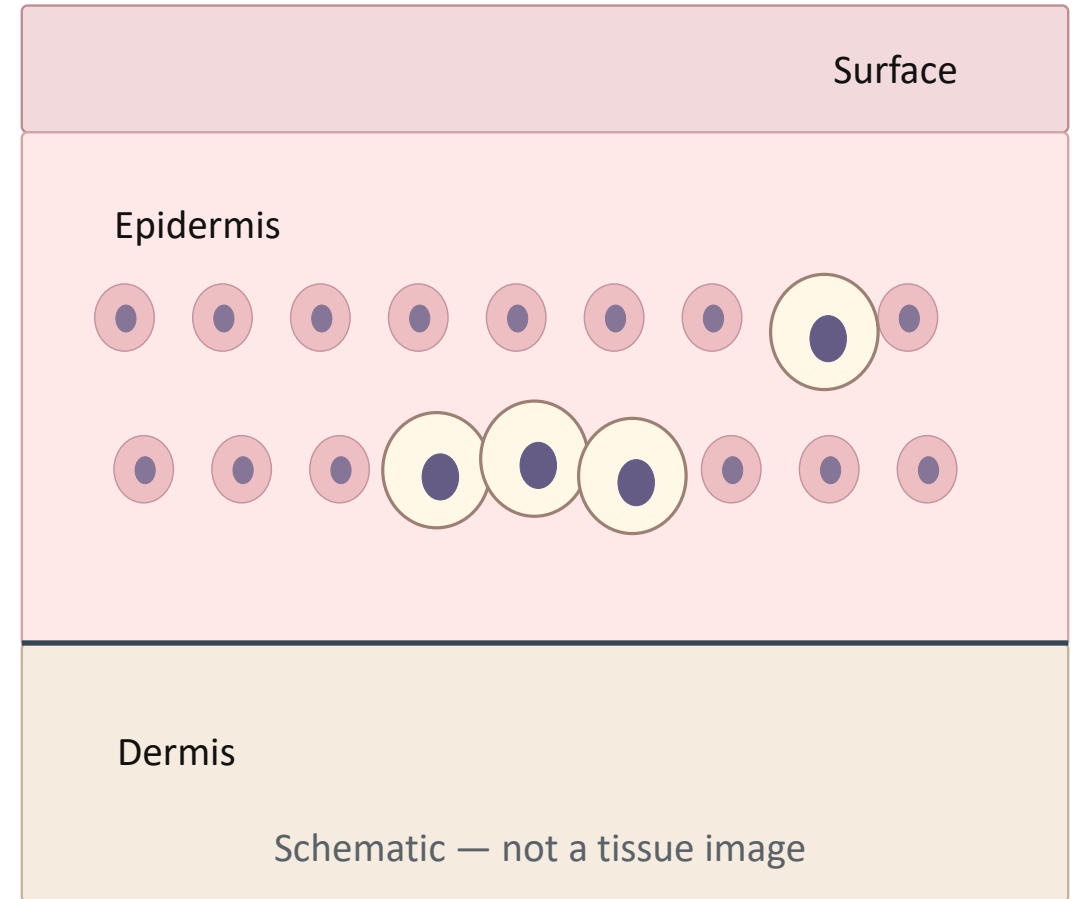
Single-cell pagetoid distribution

- Large tumor cells may occur singly among keratinocytes.
- The single-cell pattern is a diagnostic clue, not proof by itself.
- Correlate cytology with mucin and epithelial immunophenotype.



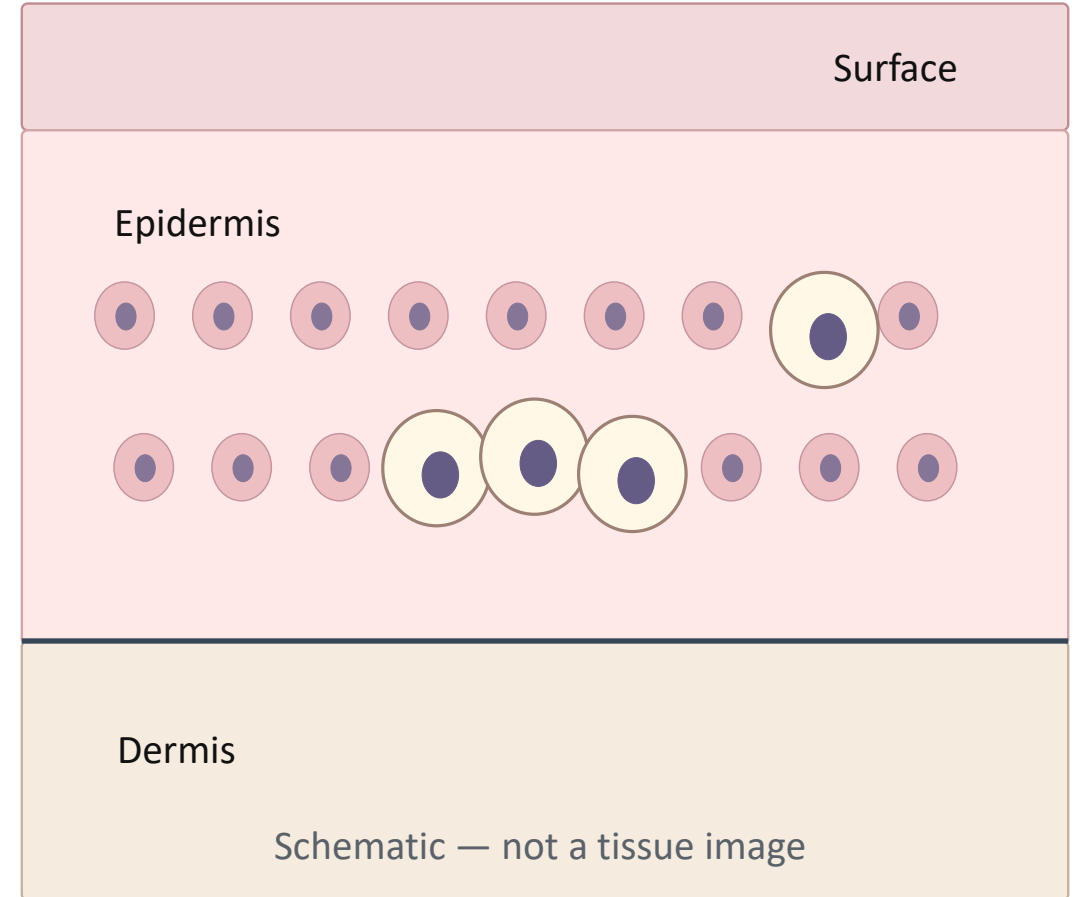
Small clusters are also characteristic

- Paget cells may form small intraepidermal groups.
- Clusters show the same pale cytoplasm as solitary cells.
- An epidermal cluster should prompt review of the underlying stroma.



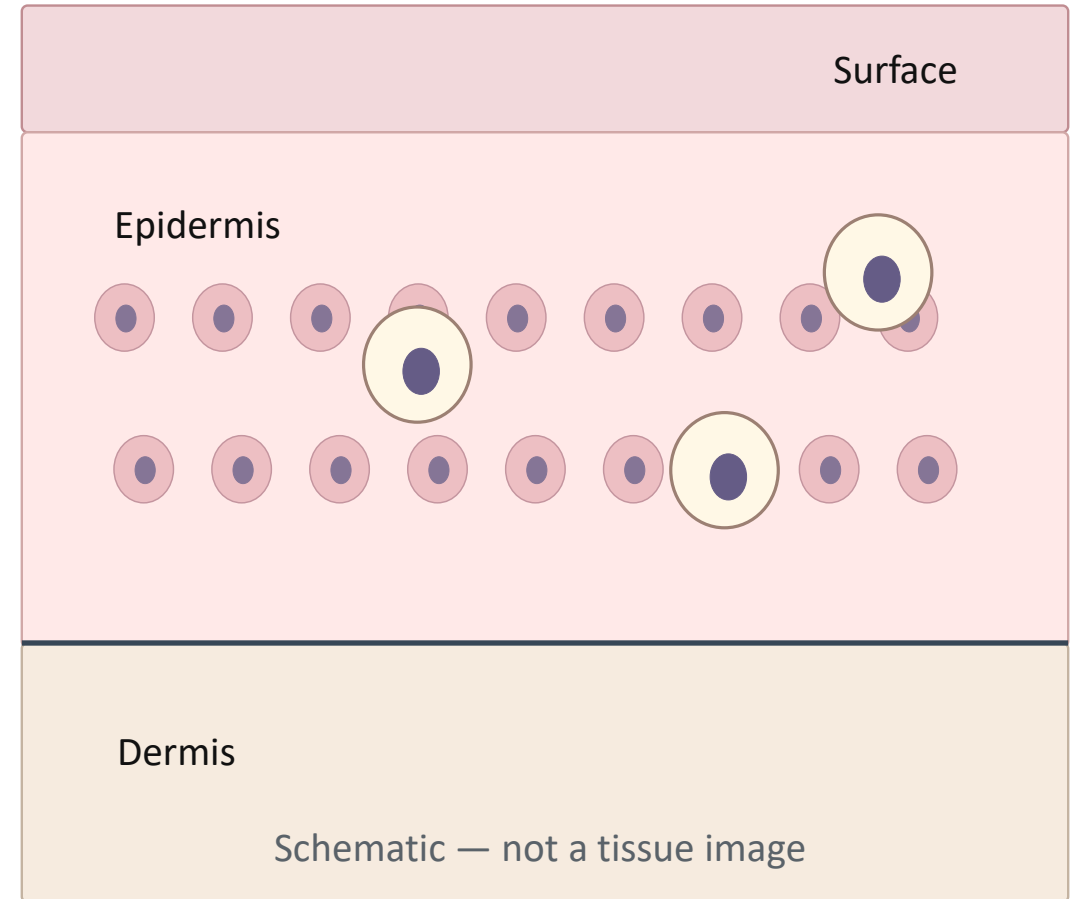
The tumor cells exceed keratinocytes in size

- Relative cell size is more useful than any absolute measurement.
- Large pale neoplastic cells interrupt a background of smaller keratinocytes.
- Atypical cells are recognized by pattern and cytology together.



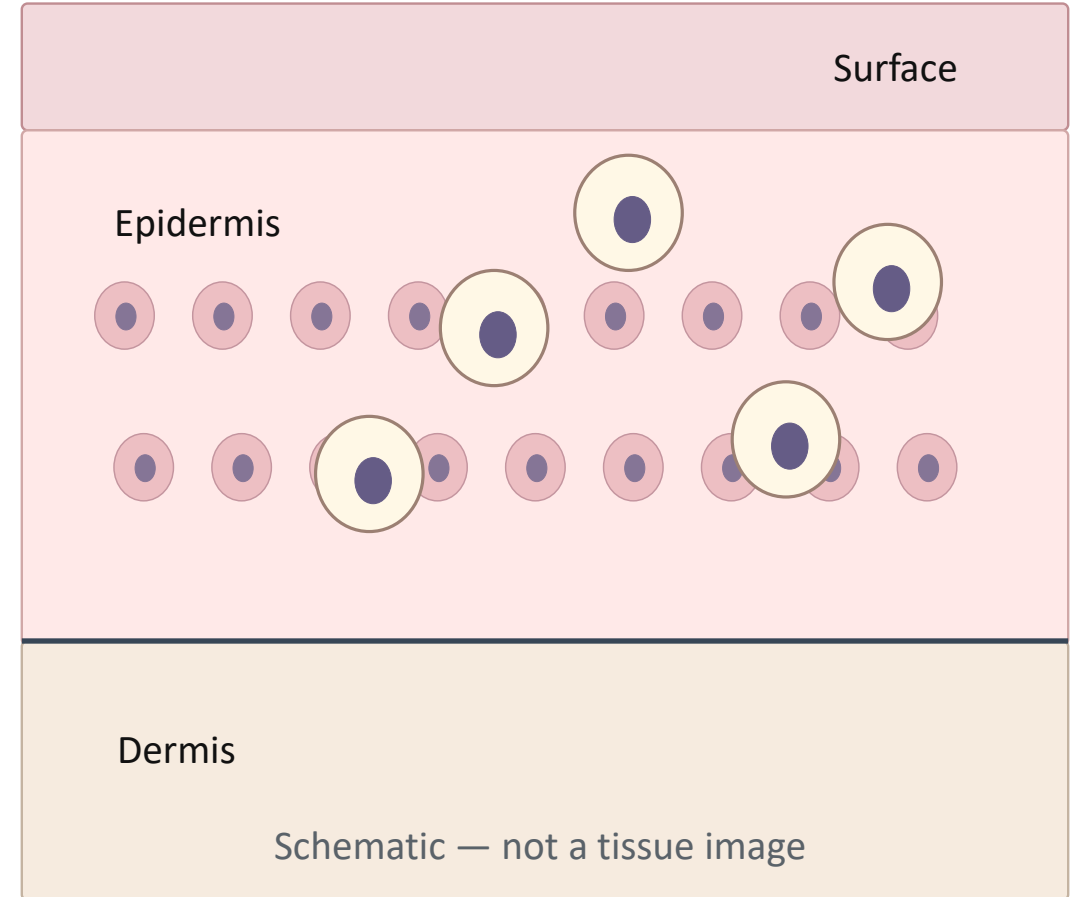
Pale cytoplasm provides the first lineage clue

- The cytoplasm often appears pale on routine sections.
- It contains mucopolysaccharide material highlighted by special stains.
- A pale-cell morphology alone is not tumor-specific.



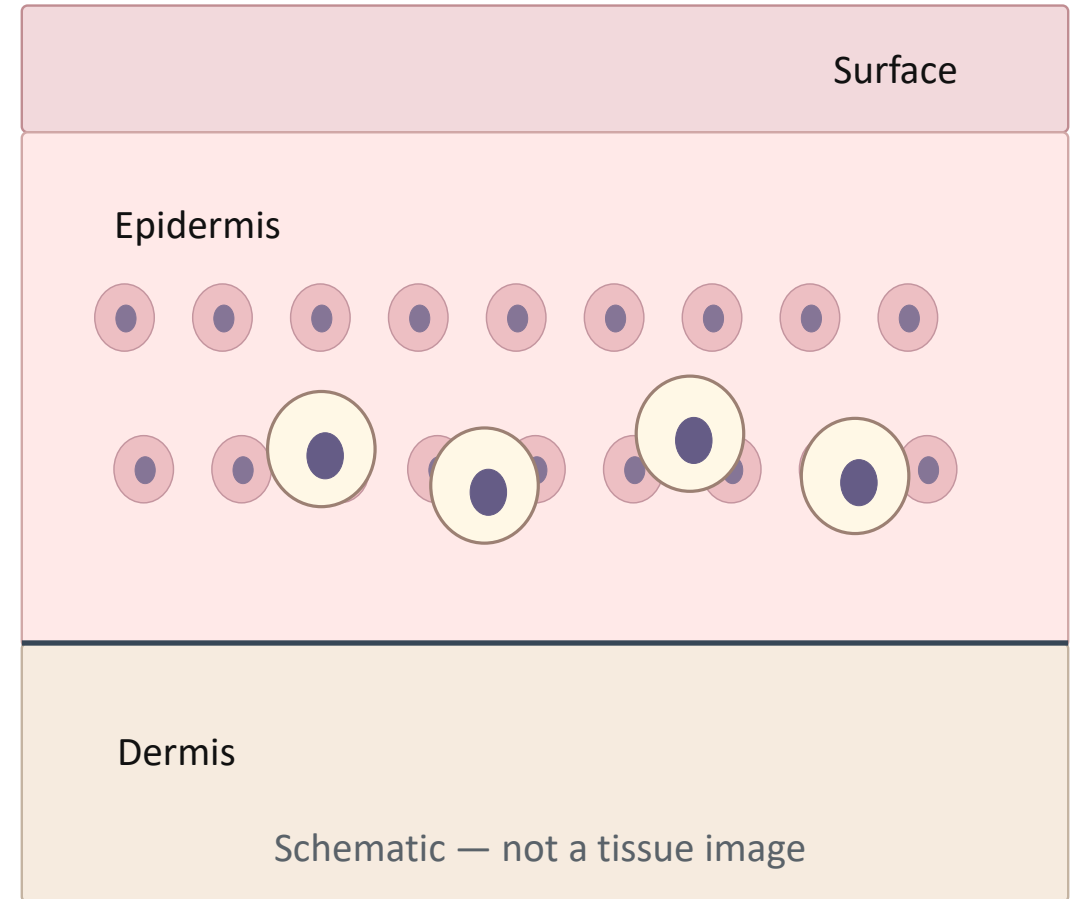
Pagetoid spread may extend upward

- Although basal growth is common, cells can occupy higher epidermal levels.
- The location of malignant cells is an architectural feature.
- Higher-level spread still need not imply dermal invasion.



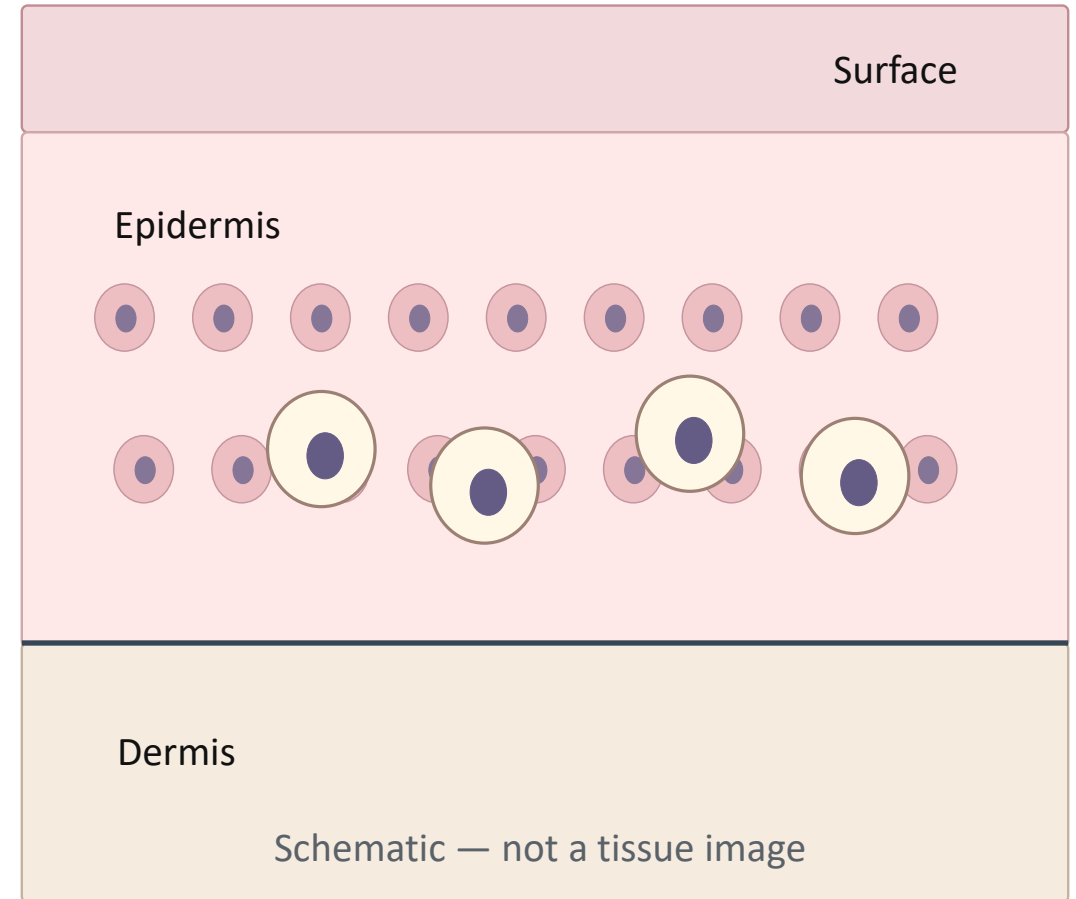
The dermis may be inflamed beneath the lesion

- Inflammation in the dermis under affected epidermis.
- An inflammatory infiltrate is not equivalent to malignant invasion.
- Distinguish reactive dermal cells from displaced malignant epithelial cells.



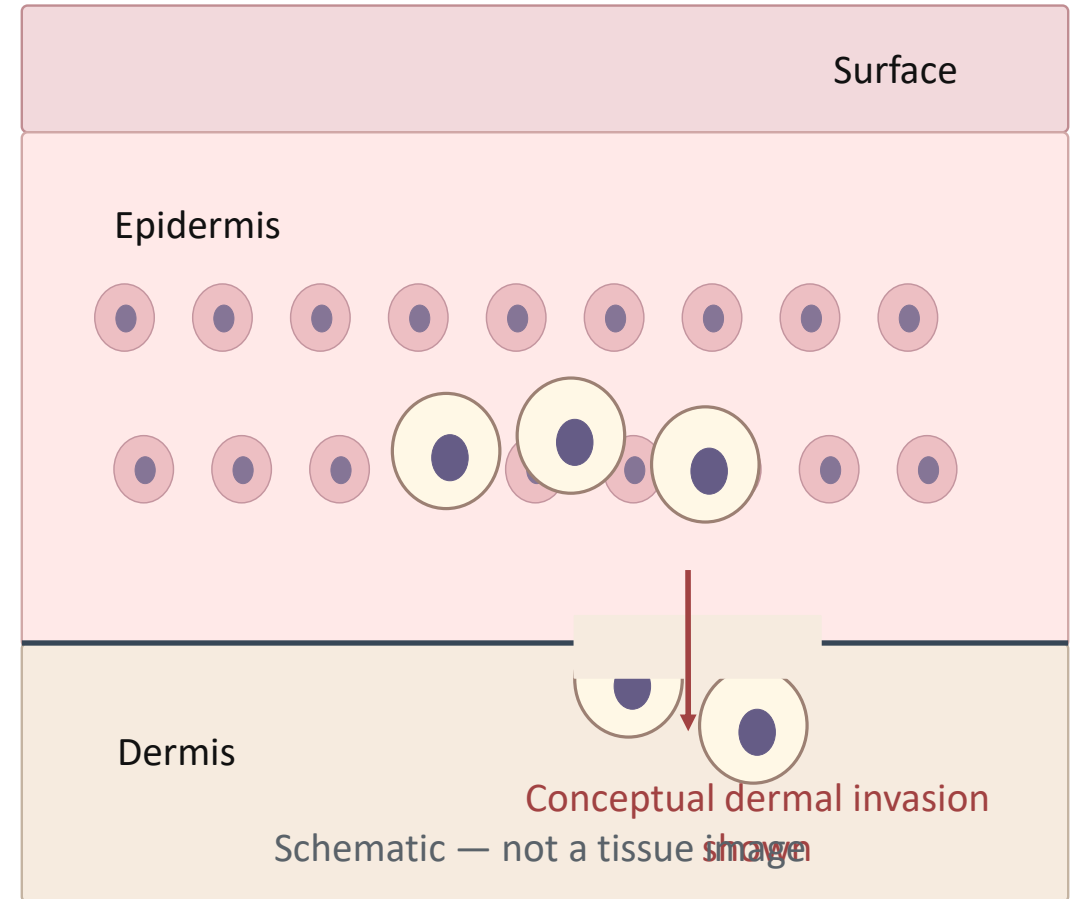
Separate epidermal and stromal compartments

- The basement membrane defines the epidermis–dermis boundary.
- Intraepidermal Paget cells lie above that boundary.
- Demonstrating actual tumor in stroma changes the classification.



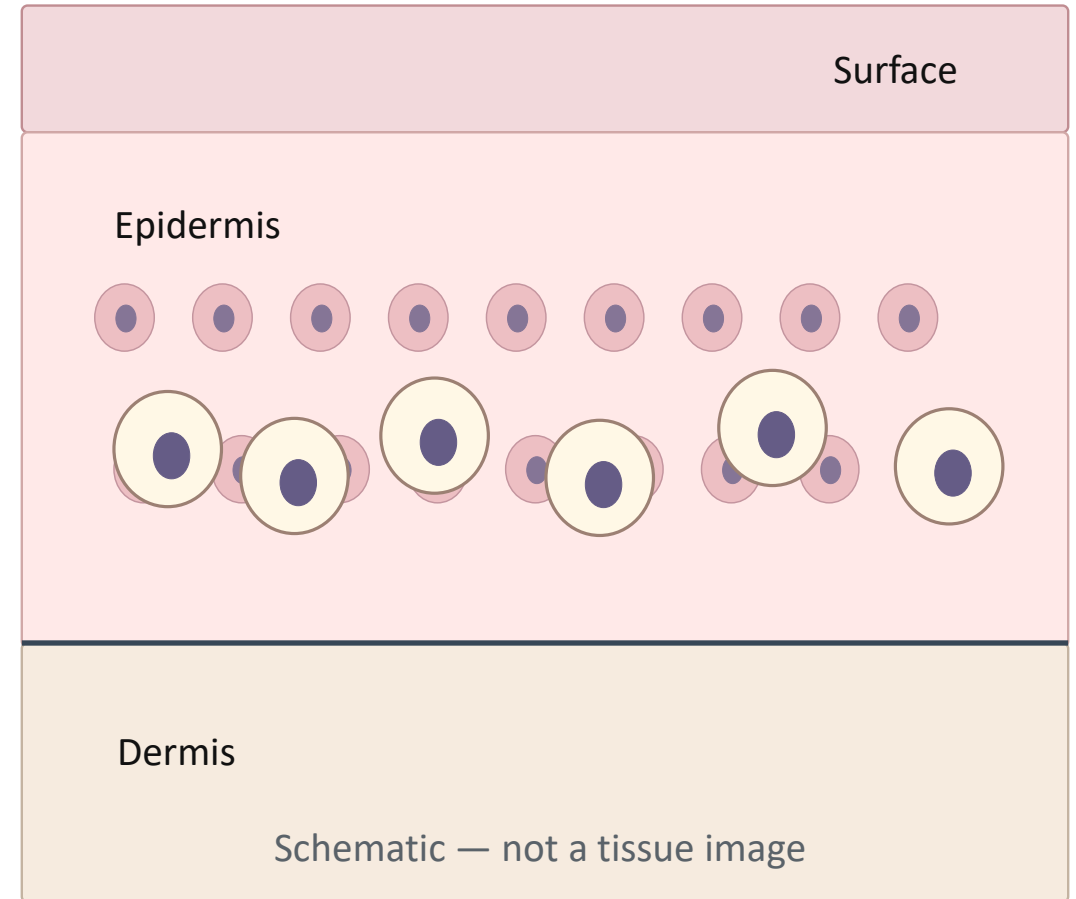
Invasion: The key pathologic question

- Microscopically identify malignant epithelial cells beyond the epidermis.
- Assess the underlying dermis rather than equating extensive epidermal spread with invasion.
- The uncommon invasive cases with poor prognosis.



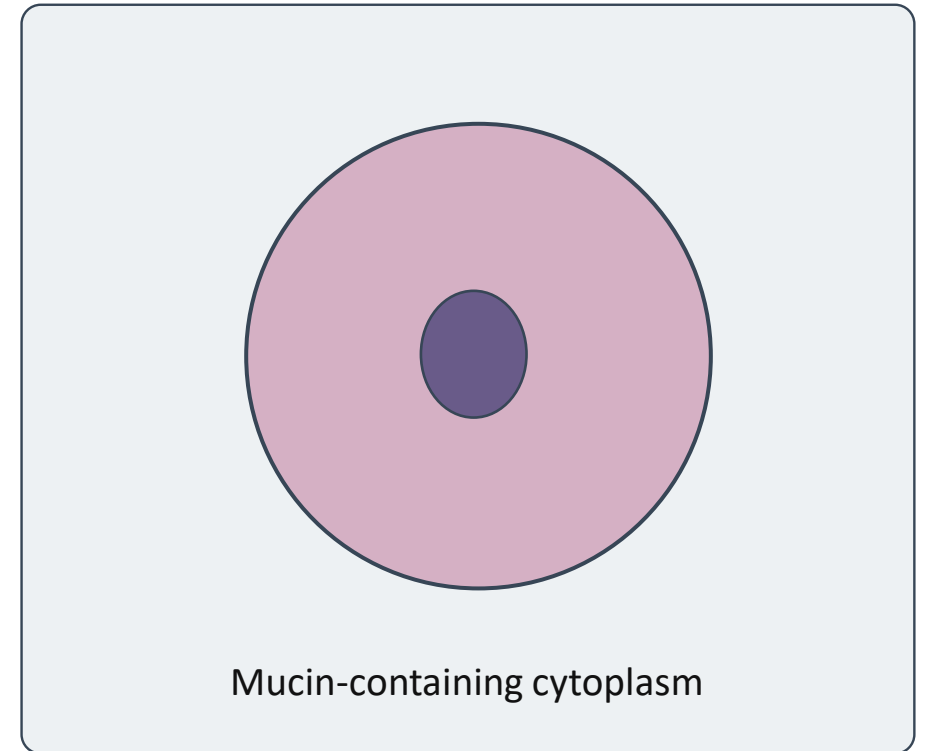
Surface spread and vertical spread are different

- Lateral spread extends the intraepidermal field horizontally.
- Vertical stromal invasion crosses the basement membrane.
- The two dimensions answer different clinical questions.



The pale cytoplasm contains mucopolysaccharide

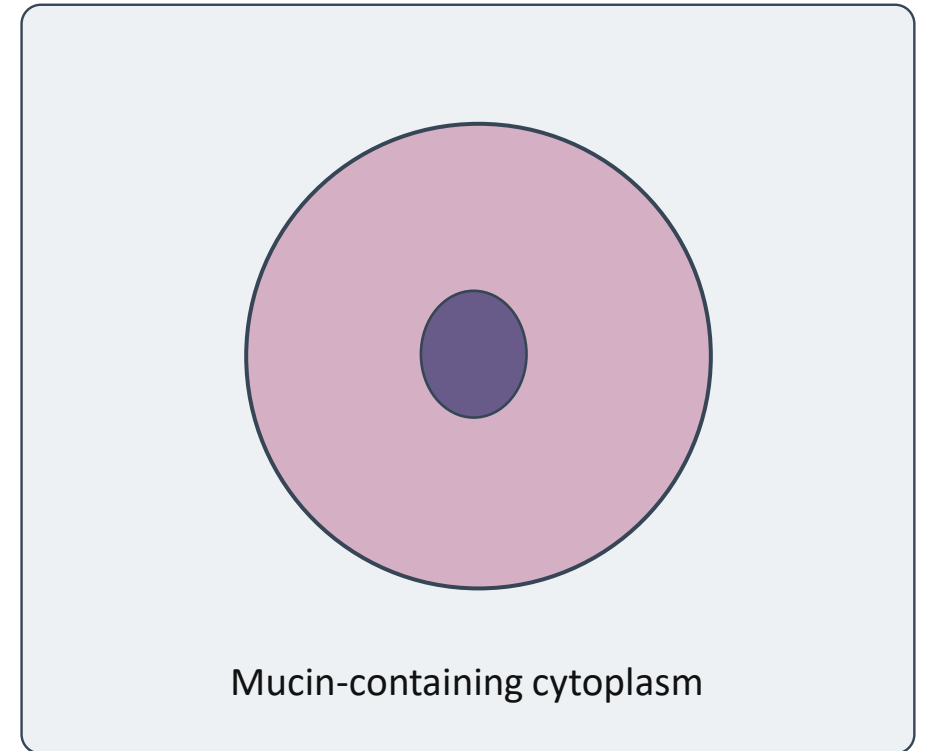
- Mucinous material explains why special stains are useful.
- The finding supports non-squamous differentiation of Paget cells.
- Its interpretation remains contingent on cell location and morphology.



PAS highlights mucopolysaccharide

Periodic acid–Schiff (PAS) stain

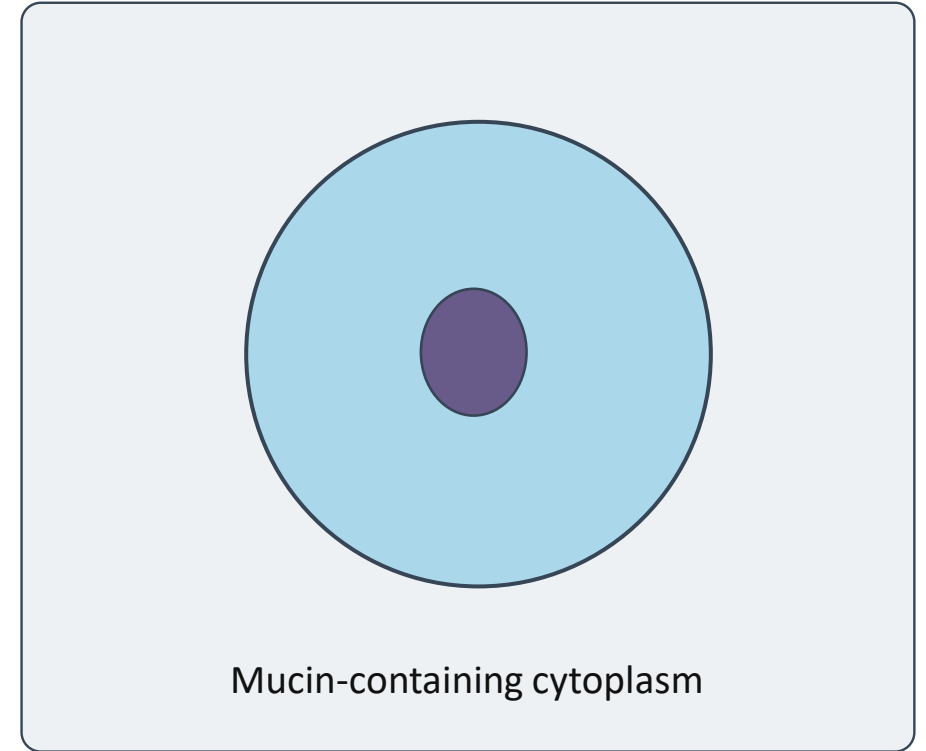
- PAS as a stain for Paget-cell mucopolysaccharide.
- A positive reaction supports intracytoplasmic mucinous material.
- It cannot, in isolation, establish the entire diagnosis.



PAS highlights mucopolysaccharide

Alcian blue highlights mucin

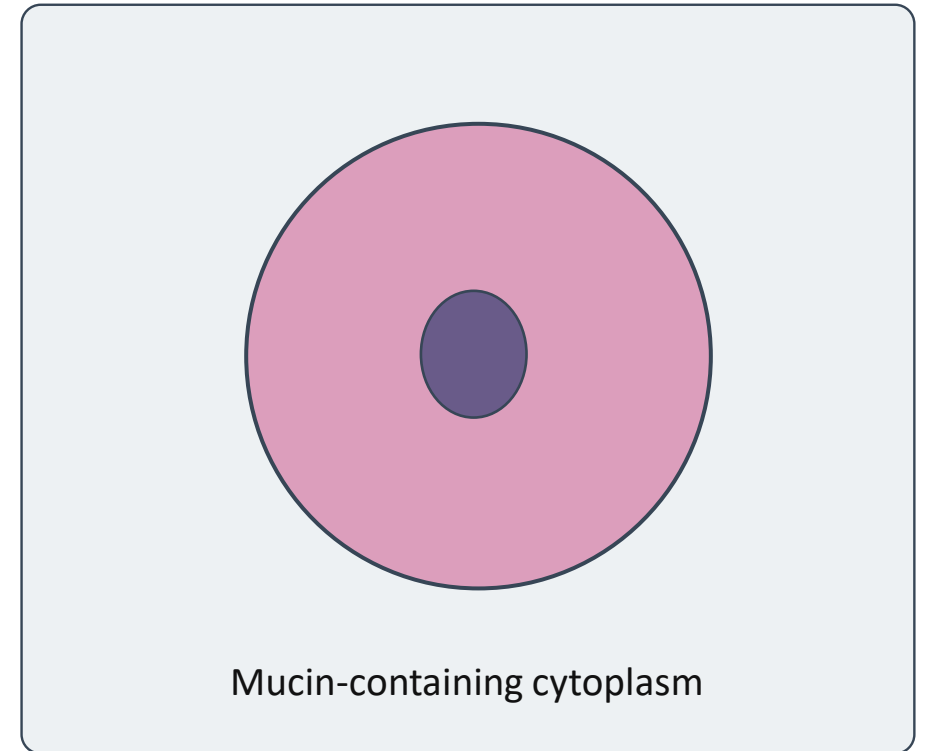
- Alcian blue is an alternative method to demonstrate mucin.
- Its role is supportive alongside H&E morphology.



Alcian blue highlights mucin

Mucicarmine: A third mucin method

- Mucicarmine can highlight mucin in Paget cells.
- The special stain demonstrates a cell product, not invasion status.
- Interpret the positive cells within their epithelial compartment.



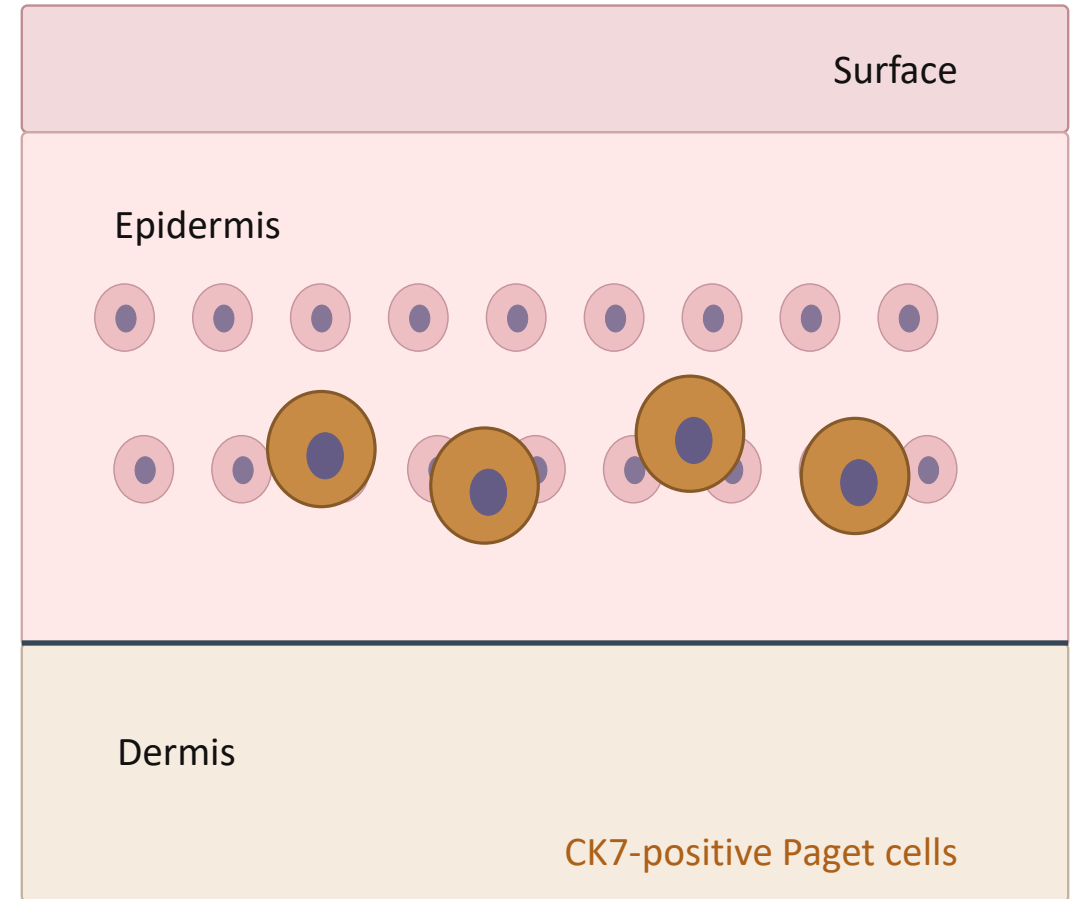
Mucicarmine highlights mucin

How to interpret the three mucin stains

Test	What it addresses	Interpretive limitation
PAS	Mucopolysaccharide in Paget-cell cytoplasm	Requires compatible morphology
Alcian blue	Mucinous cytoplasmic material	Not a stand-alone tumor classification
Mucicarmine	Mucin within Paget cells	Does not distinguish in situ from invasion

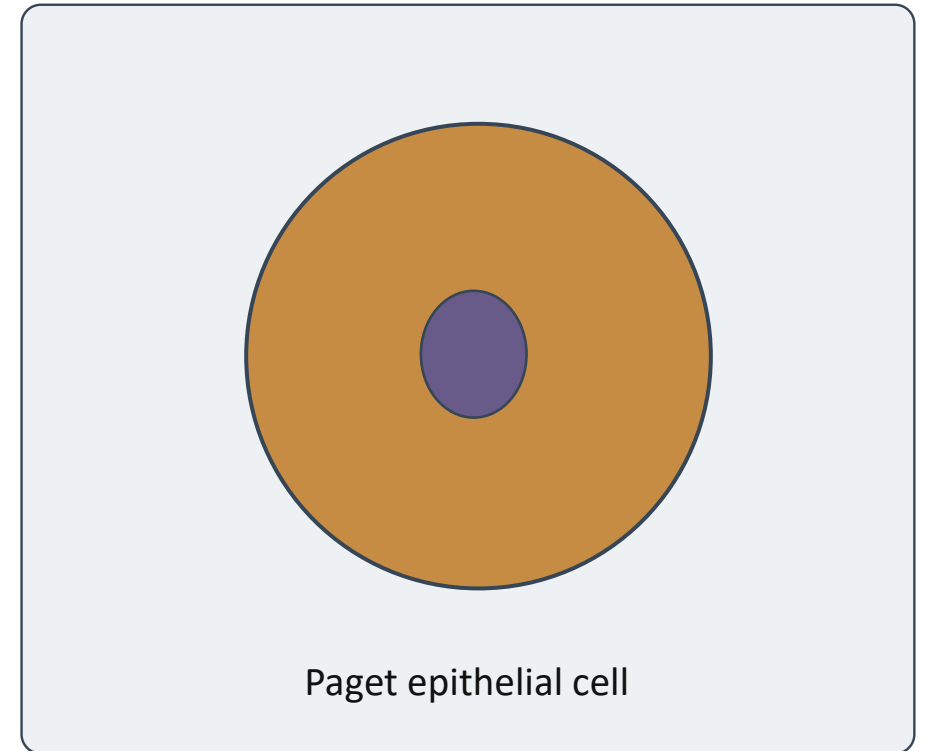
Cytokeratin 7 is a defining useful marker

- Paget cells express cytokeratin 7 (CK7).
- Ordinary surrounding squamous epithelium contrasts with this expression.
- CK7 highlights a glandular-type intraepidermal cell population.



CK7 can reveal subtle pagetoid distribution

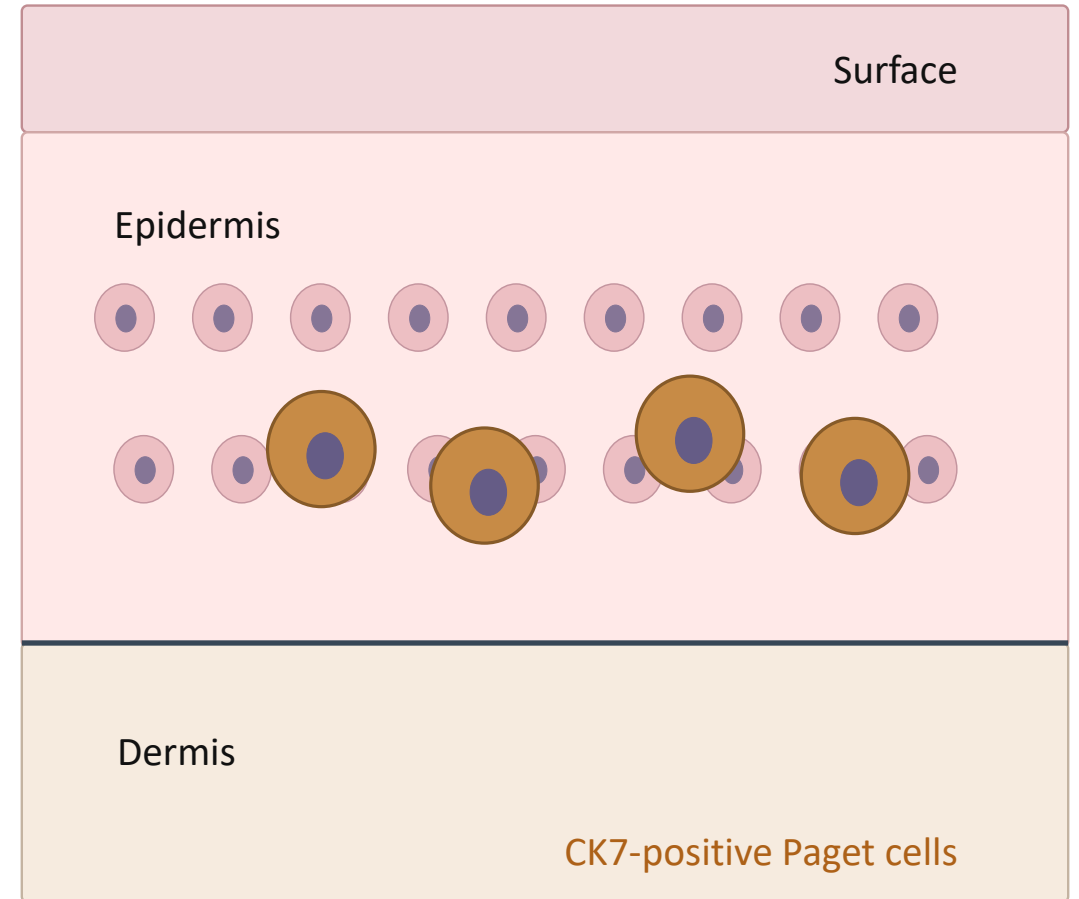
- Immunostaining makes single cells and clusters easier to localize.
- The staining pattern assists assessment of lateral epithelial extent.
- CK7 is an adjunct to the H&E architectural evaluation.



CK7 immunolabeling

Positive CK7 is not the entire differential

- Some mimics require additional lineage markers.
- A CK7-positive cell must still be evaluated in its morphologic context.
- The differential is resolved through an integrated panel, not one stain.



Morphology, mucin and CK7: Combined reasoning

Observation	Evidence contributed	What it does not prove
H&E	Pagetoid malignant cell morphology and location	Exact lineage in every case
Mucin stain	Mucopolysaccharide production	Dermal invasion
CK7	Epithelial immunophenotype and cell mapping	Primary versus secondary origin

Ultrastructural differentiation is mixed

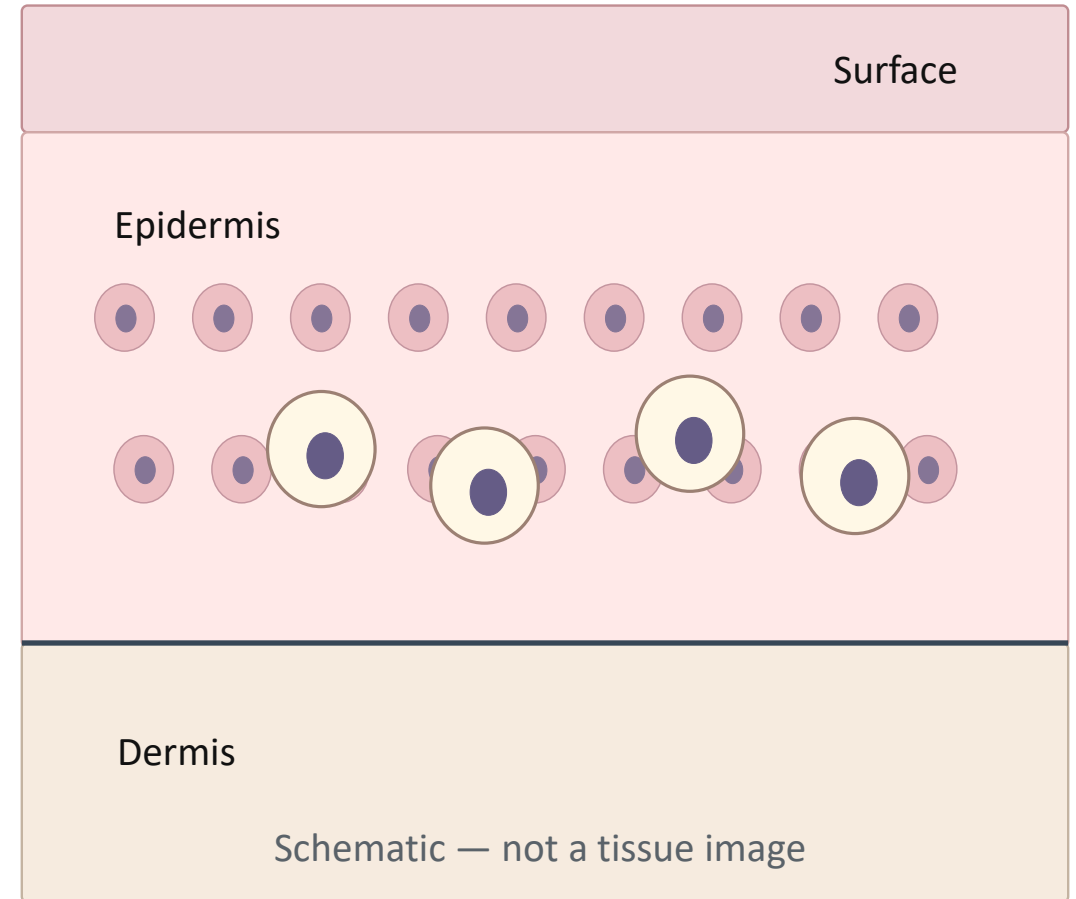
- Apocrine, eccrine and keratinocyte differentiation.
- The phenotype suggests biologic plasticity of these cells.
- This does not require every case to reproduce each feature.

The proposed cell of origin is a hypothesis

- Multipotent cells in mammary gland–like vulvar ducts.
- The wording is presumptive, not proof of an established origin.
- Do not equate this proposal with demonstrated causation.

Paget disease is a pattern shared across sites

- Mammary and extramammary disease share pagetoid epidermal morphology.
- Their usual relationships to underlying carcinoma differ.
- A histologic image without anatomic context cannot establish the site.



Vulvar versus mammary Paget disease

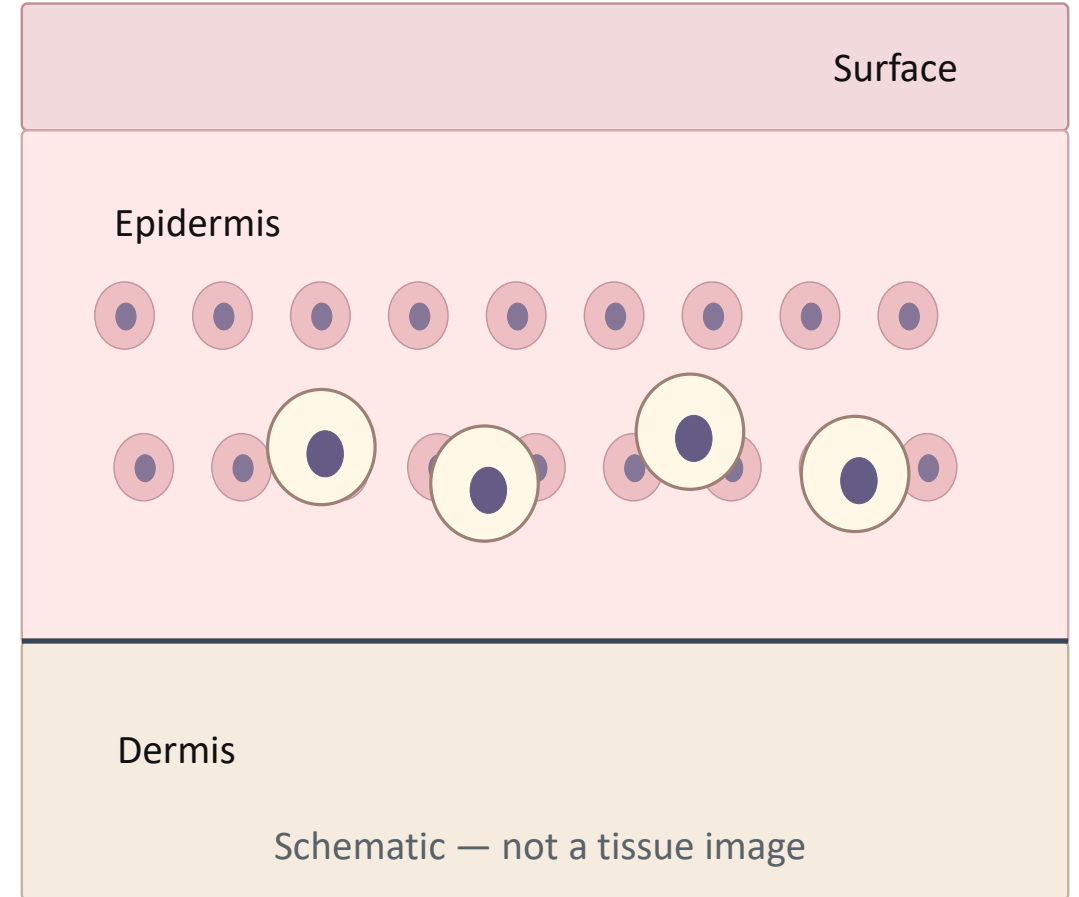
Feature	Vulvar Paget disease	Mammary Paget disease
Typical site	Vulvar epidermis; Often labia majora	Nipple–areolar epidermis
Association	Often no underlying cancer	Associated with ductal breast carcinoma
Anatomic model	Intraepithelial vulvar tumor	Tumor spread from ducts toward nipple skin
Shared pattern	Large pale epidermal Paget cells	Large pale epidermal Paget cells

Mammary Paget: Connection to ductal carcinoma

- In breast, Paget cells extend from ductal carcinoma in situ.
- Cells migrate through lactiferous ducts into nipple epidermis.
- The neoplastic cells can remain above the basement membrane.

Vulvar Paget: Association is different

- That vulvar Paget disease often lacks underlying cancer.
- Most cases are confined to vulvar epidermis.
- The contrast is typical, not a statement that associations are impossible.

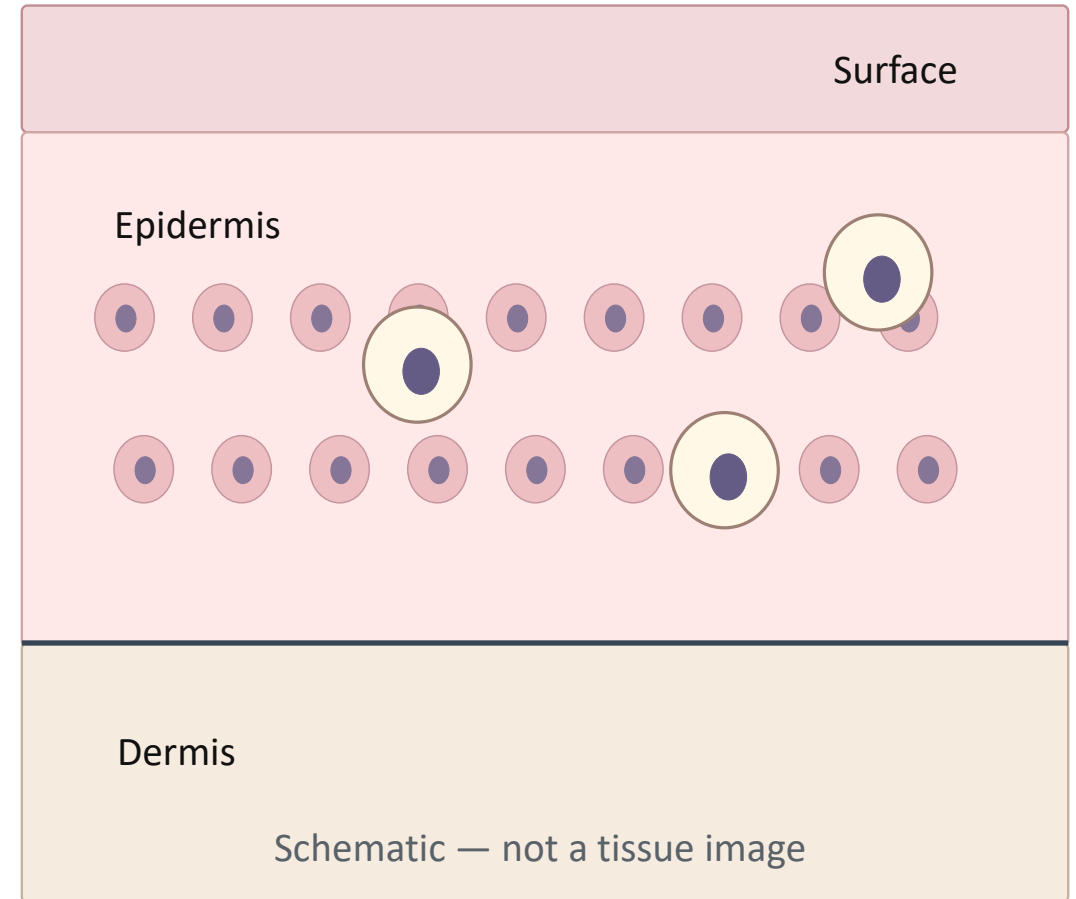


An associated internal malignancy remains a consideration

- Some extramammary Paget presentations relate to underlying internal cancer.
- Primary skin disease and secondary epidermal involvement are different questions.
- Site-specific evaluation must follow the actual clinical findings.

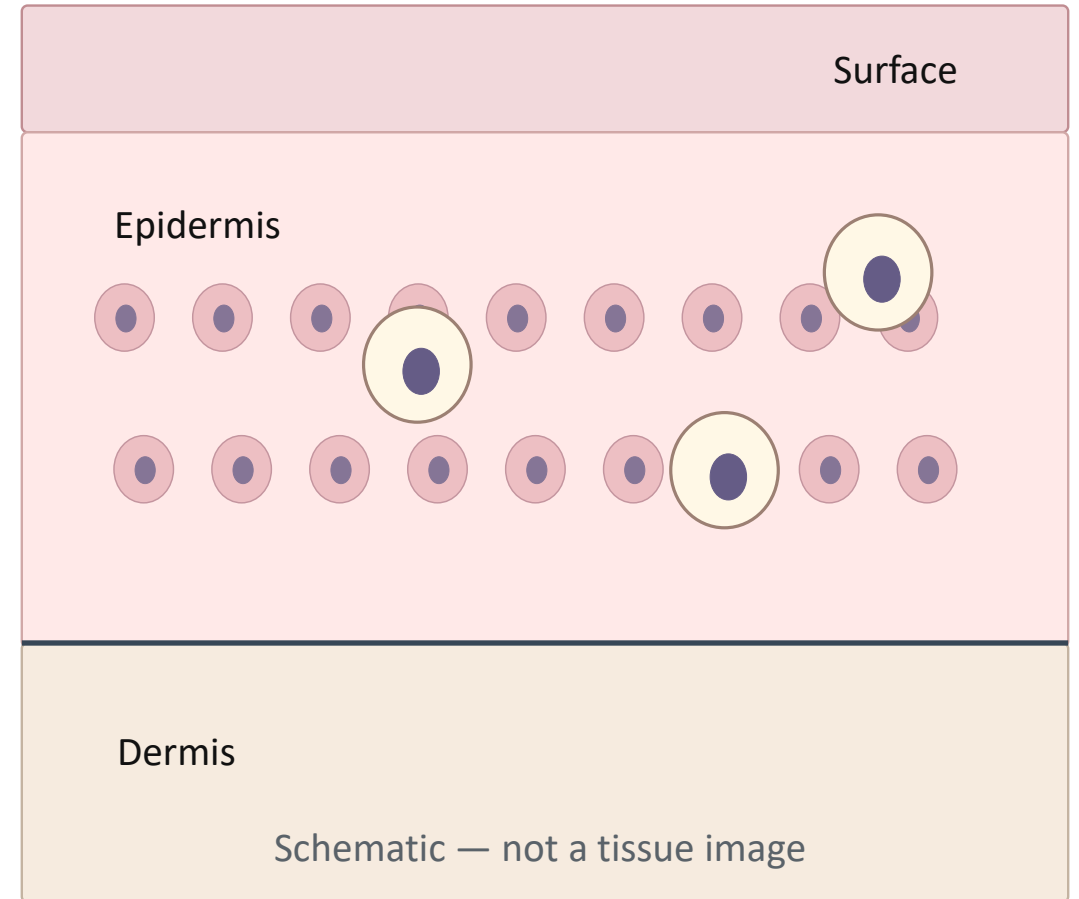
The main microscopic mimics are lineage-defined

- Pagetoid melanoma may place atypical cells within epidermis.
- Squamous cell carcinoma in situ may also show intraepithelial atypia.
- Ancillary markers help establish melanocytic versus squamous versus glandular lineage.



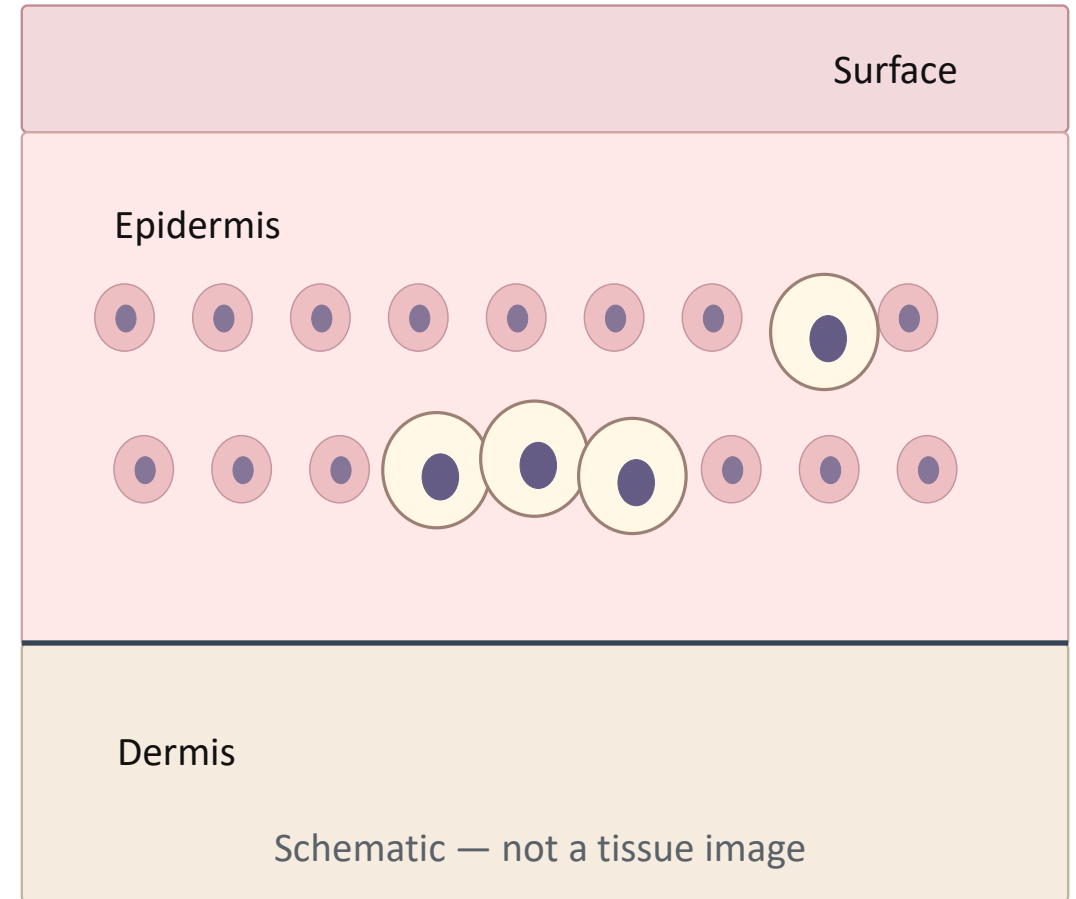
Melanoma in situ: A major pagetoid mimic

- Melanocytic lesions can contain atypical intraepidermal cells.
- Paget disease expresses epithelial keratins; Melanoma is typically melanocytic-marker positive.
- Use a panel with morphology rather than an isolated marker.



Squamous cell carcinoma in situ: Key contrast

- Squamous intraepithelial carcinoma reflects a keratinocyte phenotype.
- P63 supports squamous differentiation, whereas mucin favors Paget cells.
- CK7 alone is not sufficient to exclude squamous intraepithelial carcinoma.

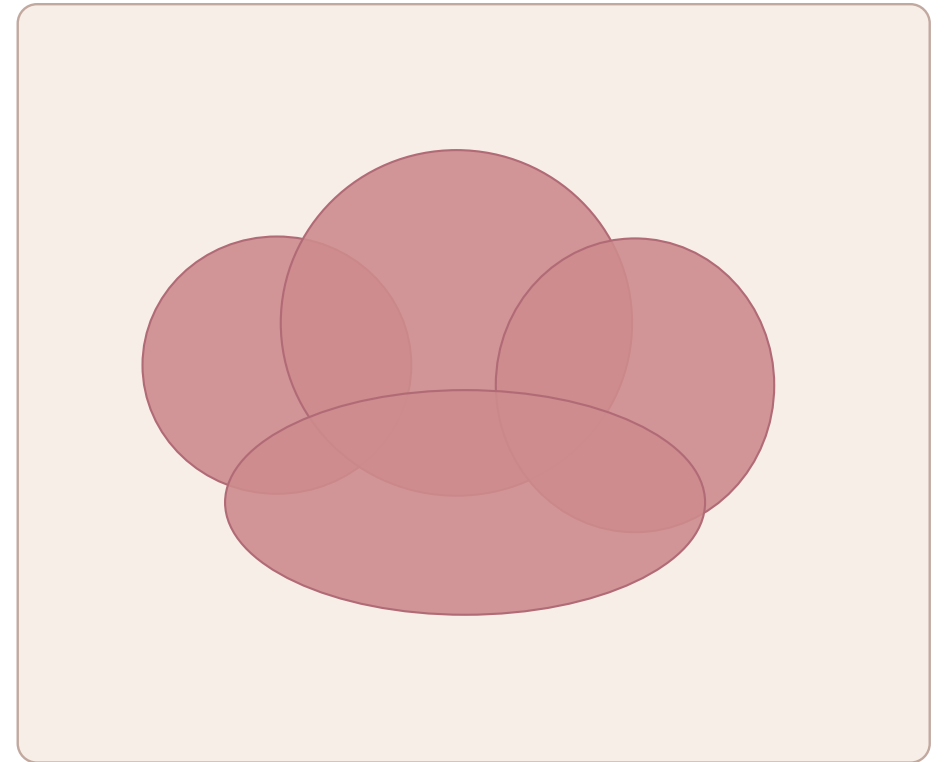


Pagetoid differential: Practical immunophenotype

Feature	Paget disease	Melanoma in situ	SCC in situ
Cell identity	Glandular-type epithelial	Melanocytic	Squamous
Useful supportive stain	CK7 and mucin stains	S100 / SOX10 or Melan-A	P63 / p40
Interpretation	Integrate cells and site	Exclude epithelial mimic	Account for CK7 overlap

The eczema-like appearance is a diagnostic trap

- Clinical inflammation can resemble the crusted pruritic plaque.
- Histologic pagetoid malignant cells distinguish the neoplasm.
- Failure to assess a persistent lesion can delay recognition.



Pruritic erythematous plaque (schematic)

Papillary hidradenoma is glandular but different

- Papillary hidradenoma is a circumscribed vulvar nodule.
- Its papillae contain luminal secretory and basal myoepithelial cells.
- Paget disease instead consists of malignant cells within epidermis.

Two vulvar glandular-type lesions

Feature	Extramammary Paget	Papillary hidradenoma
Clinical tendency	Crusted/pruritic plaque	Circumscribed nodule
Main compartment	Epidermis	Dermal glandular tumor
Microscopic pattern	Single cells and clusters	Papillary projections; Dual cell layer
Management logic	Address occult lateral spread	Assess localized nodular lesion

Squamous vulvar neoplasia is a separate pathway

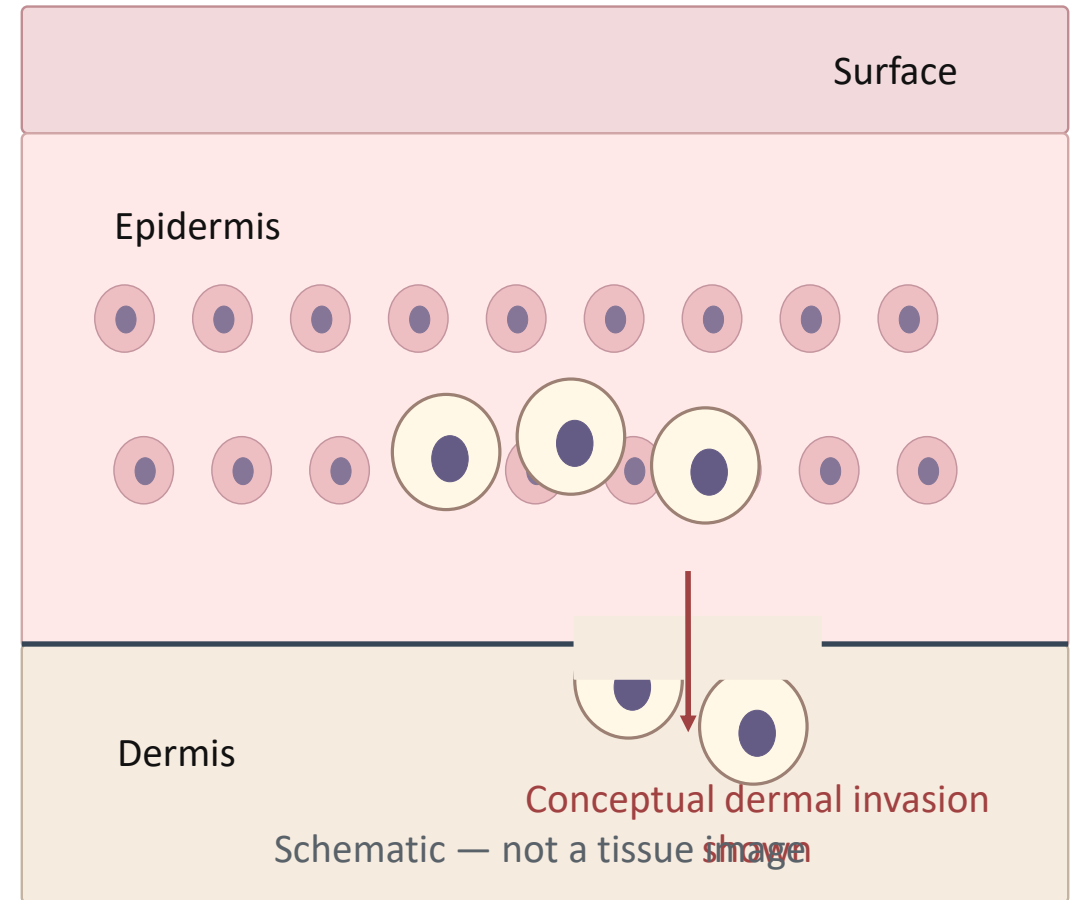
- VIN and invasive SCC are squamous epithelial neoplasms.
- Paget disease has characteristic mucinous pale epithelial cells.
- Do not automatically apply HPV-driven squamous tumor biology to Paget disease.

Diagnostic sequence: Pattern before immunostains

- Identify an atypical intraepidermal pale-cell population.
- Confirm glandular-type differentiation with CK7 and mucin, as needed.
- Use additional markers when the pagetoid differential remains open.

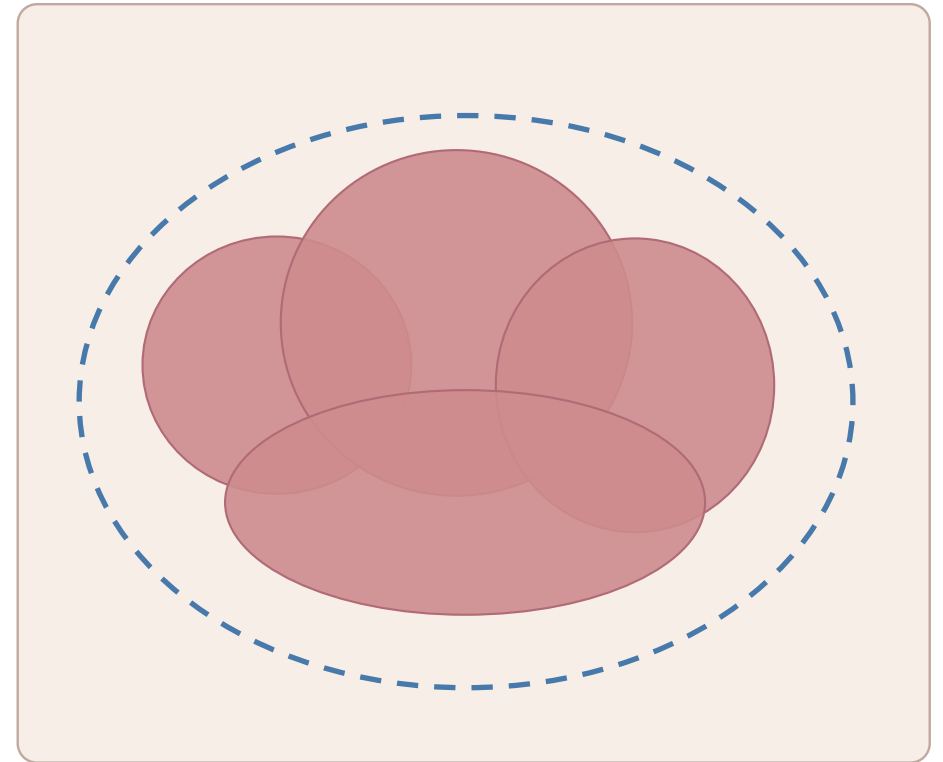
Diagnostic sequence: Decide whether invasion exists

- Review the epidermal–dermal interface carefully.
- Separate intraepidermal malignant cells from stromal cells.
- Describe true dermal involvement when supported by tissue findings.



Microscopic lateral spread can be invisible

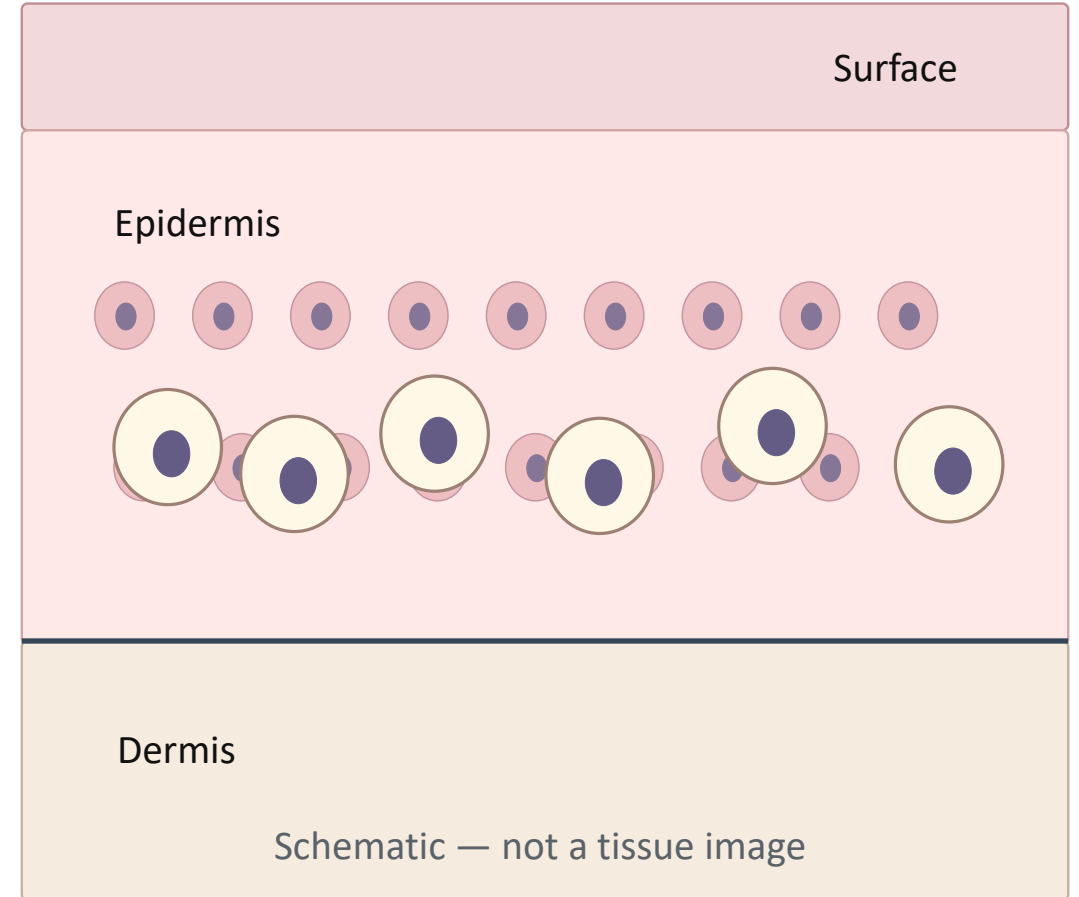
- Paget cells may extend beyond the grossly affected skin.
- The pathologic boundary may exceed the red, crusted plaque.
- This is the rationale for careful excision planning.



Dashed outline: Conceptual microscopic extent

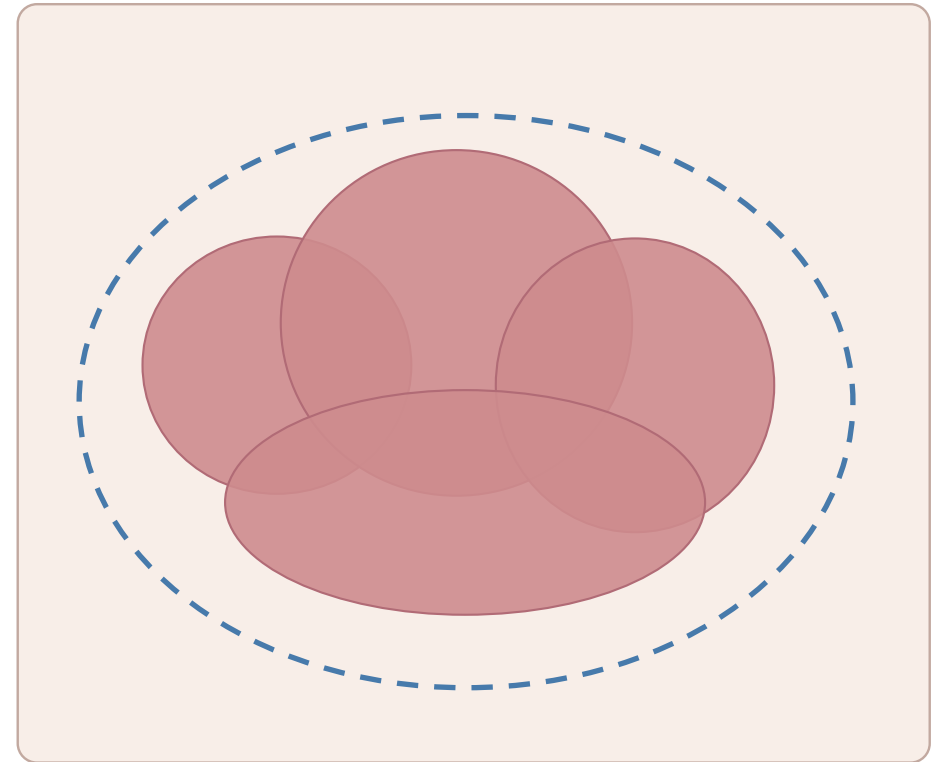
Excision margin assessment follows cell distribution

- Lateral epidermal involvement is a practical margin issue.
- A specimen needs orientation and careful edge evaluation.
- Clear-looking skin does not, by itself, establish a negative margin.



Wide local excision addresses occult spread

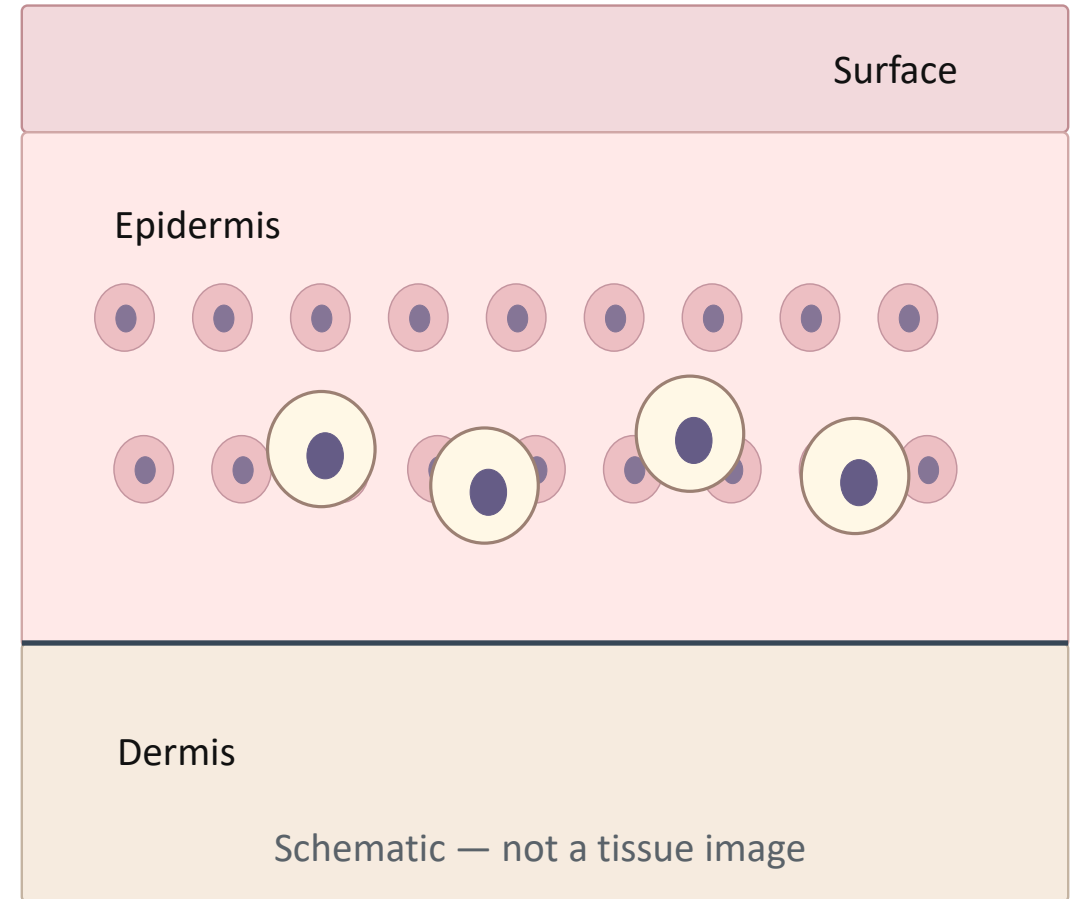
- Wide local excision as treatment.
- The justification is microscopically extensive lateral epidermal spread.
- Histopathologic mapping and margins matter for local clearance.



Dashed outline: Conceptual microscopic extent

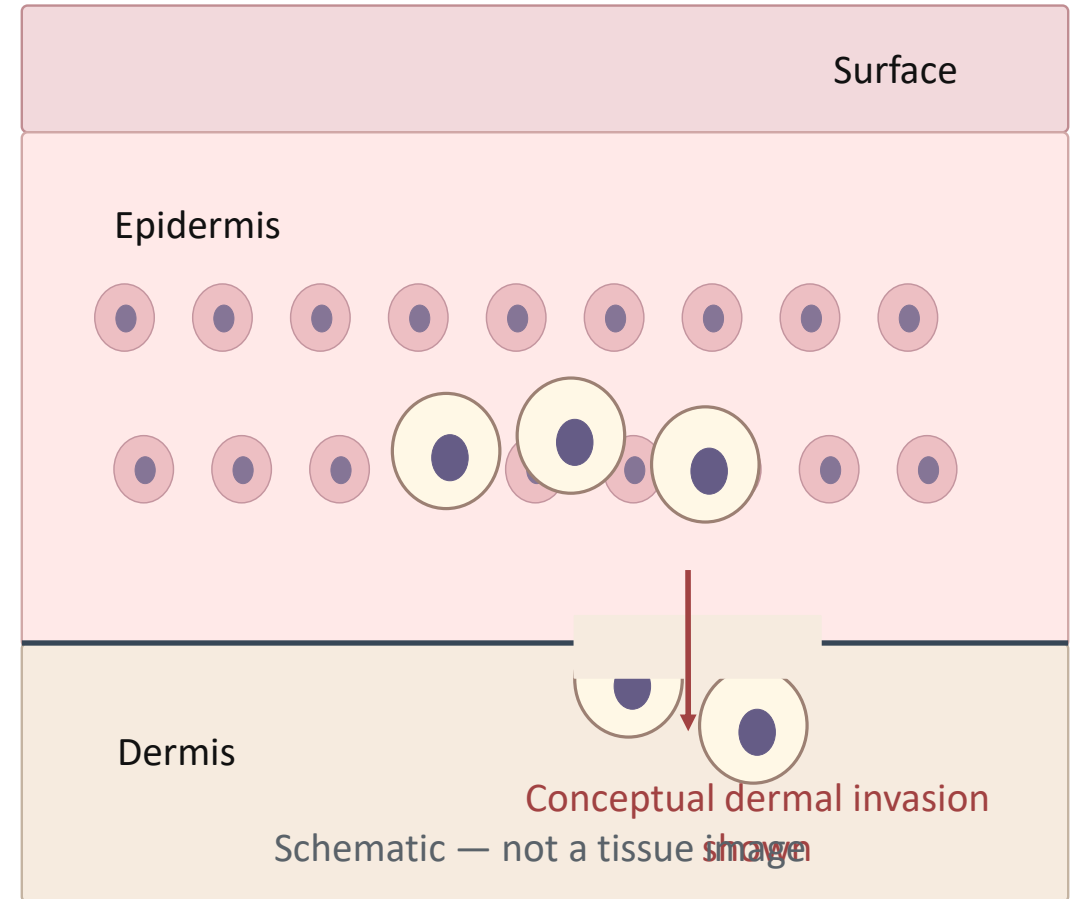
A long intraepidermal course is possible

- Disease restricted to epidermis may persist for years or decades.
- Persistence does not necessarily imply early invasion.
- Prolonged local disease still carries a clinical burden.



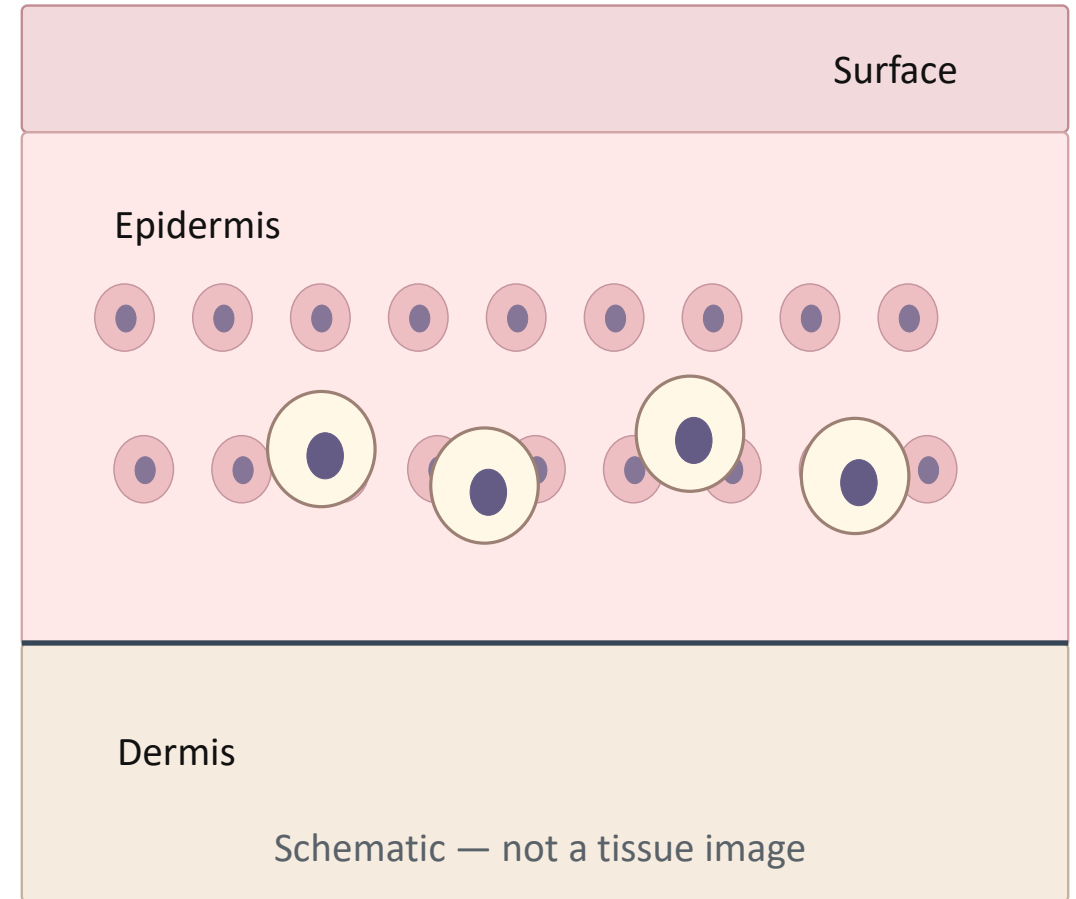
Dermal invasion is uncommon but consequential

- Invasive progression as rare.
- Prognosis becomes poor when invasion develops.
- Separate long-lasting in situ disease from the invasive subset.



Avoid misinterpreting the word malignant

- Paget cells are malignant even when confined to epidermis.
- Malignancy and stromal invasion are not synonymous.
- Precise reports should state epithelial confinement or invasion.



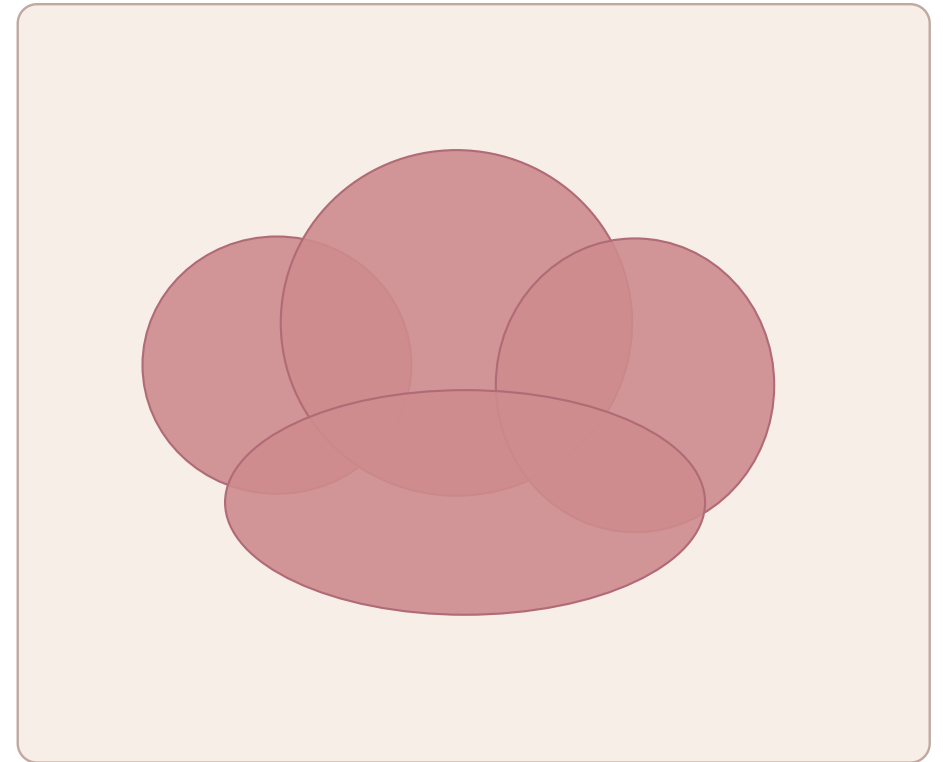
Four clinical questions answer different things

Question	Tissue or clinical evidence	Clinical consequence
Where is the disease?	Site and lesion mapping	Directs examination and sampling
What cells are present?	H&E, mucin, CK7 $\pm$ differential panel	Defines the lesion
Does it invade?	Epidermal–dermal interface	Changes biologic interpretation
How far does it extend?	Lesion extent and margins	Informs excision

Case 1: A persistent vulvar plaque

A patient has a slowly enlarging, pruritic, red, crusted lesion of the labia majora. The clinical border is irregular.

- What diagnosis belongs in the differential?
- What additional assessment is necessary?

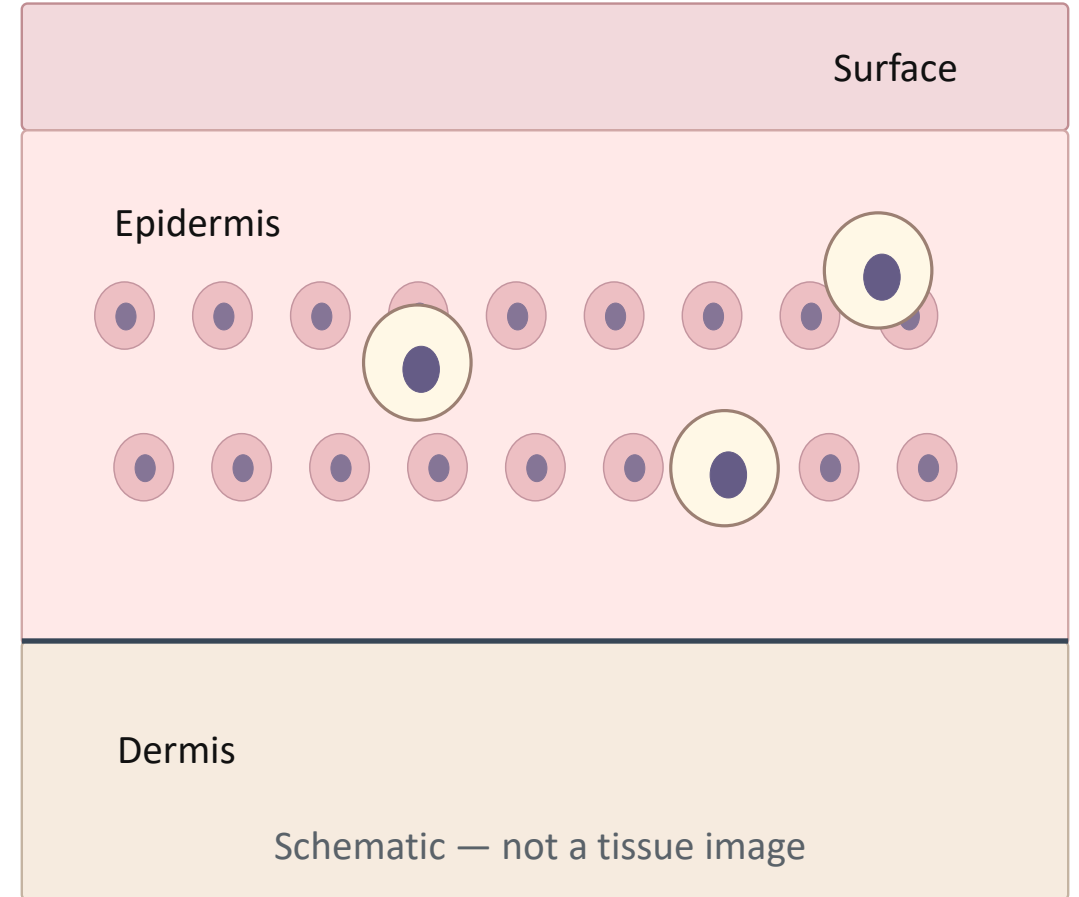


Pruritic erythematous plaque (schematic)

Case 2: Atypical cells within epidermis

Biopsy shows large pale cells, singly and in small groups, among the squamous epidermal keratinocytes. The underlying dermis is inflamed.

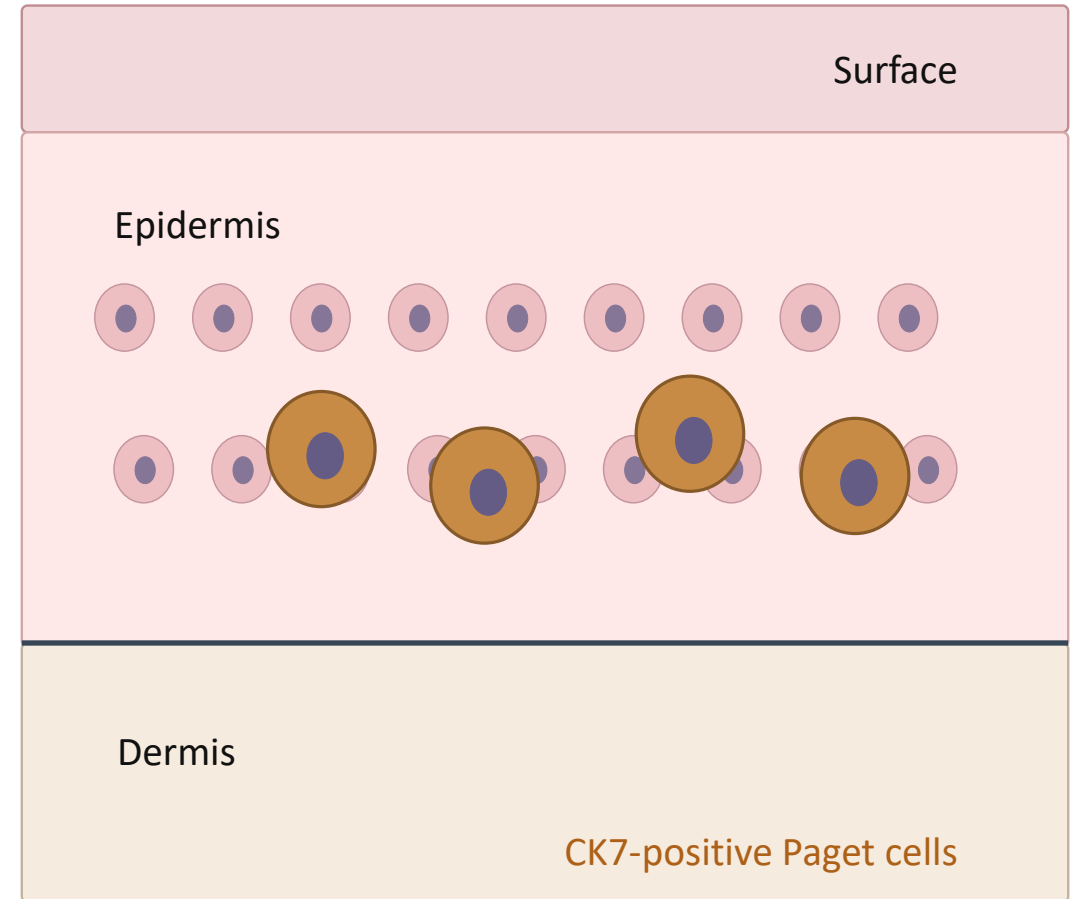
- Name the characteristic architecture.
- Does inflammation alone prove invasion?



Case 3: Interpreting an immunostain

The pale epidermal cells express CK7; Mucin can be highlighted by special stains.

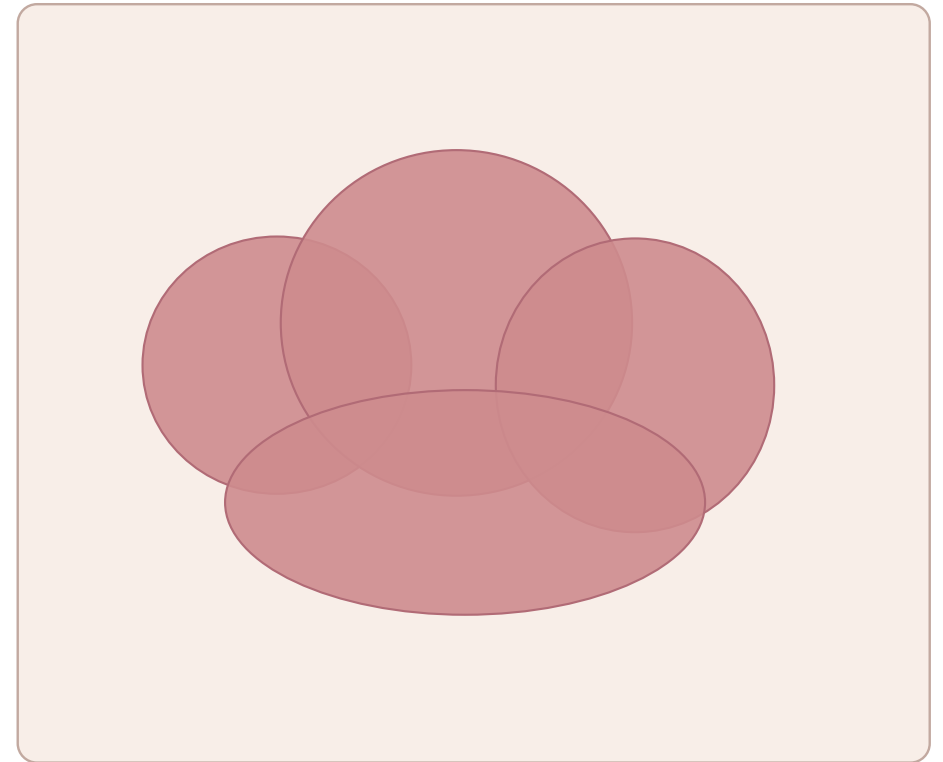
- Which cell lineage is supported?
- Why must H&E and the clinical site still be reviewed?



Case 4: A lesion wider than it looks

Excision planning is challenged by microscopic Paget cells appearing beyond the grossly evident plaque.

- Explain the mechanism of the mismatch.
- What treatment rationale follows?



Pruritic erythematous plaque (schematic)

Reporting priorities in a pathology discussion

- Identify Paget cells and their intraepidermal distribution.
- Record invasion status only when assessable in sampled tissue.
- Communicate the relevance of lesion and margin extent.

Frequent diagnostic reasoning errors

- Calling an eczematous plaque benign from appearance alone.
- Treating CK7 as infallibly specific without a differential.
- Mistaking dermal inflammation for malignant invasion.
- Assuming visible borders equal microscopic borders.

Knowledge check: Interpret the observation

Observation	Most defensible inference
Isolated pale cells within vulvar epidermis	Consider Paget disease; Evaluate morphologic differential
PAS / Alcian blue / mucicarmine positivity	Supports mucinous cytoplasm
CK7 positive intraepidermal cells	Supports Paget phenotype in context
Malignant cells crossing into dermis	Invasive component; Higher concern

Knowledge check: Choose the next step

- Pruritic vulvar plaque persisting despite ordinary measures: Tissue evaluation rather than clinical assumption.
- Pagetoid malignant cells with uncertain lineage: Appropriate lineage immunostains.
- CK7-positive epidermal neoplasm: Examine H&E architecture and the underlying dermis.
- Grossly confined plaque: Remember possible microscopic lateral extension.

Core clinicopathologic synthesis

Vulvar pruritic / crusted plaque



Intraepidermal pale malignant cells

Microscopic lateral extension



Mucin-containing cytoplasm + CK7

Assess invasion and excision extent

Selected source references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 22: The Female Genital Tract, pp. 902–903.
- Robbins, Cotran & Kumar. 11th ed. 2026. Chapter 23: The Breast, pp. 952–953 (mammary comparison).
- Cheng H, Lamont D. Extramammary Paget disease pathology. DermNet (2014). <https://dermnetnz.org/topics/extramammary-paget-disease-pathology>