# CUTANEOUS METASTSES, PAGET DISEASE, AND LEUKEMIA CUTIS

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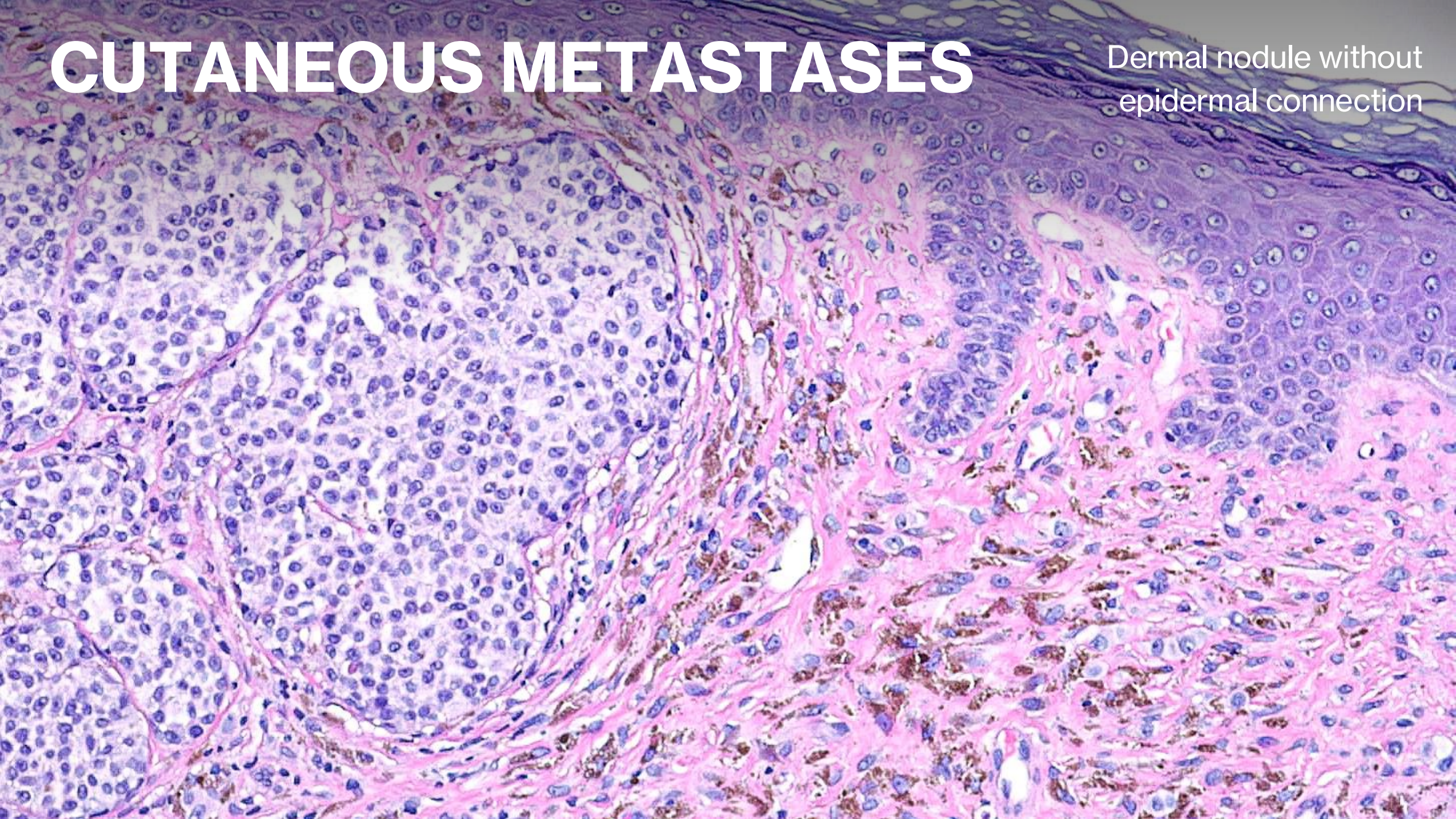
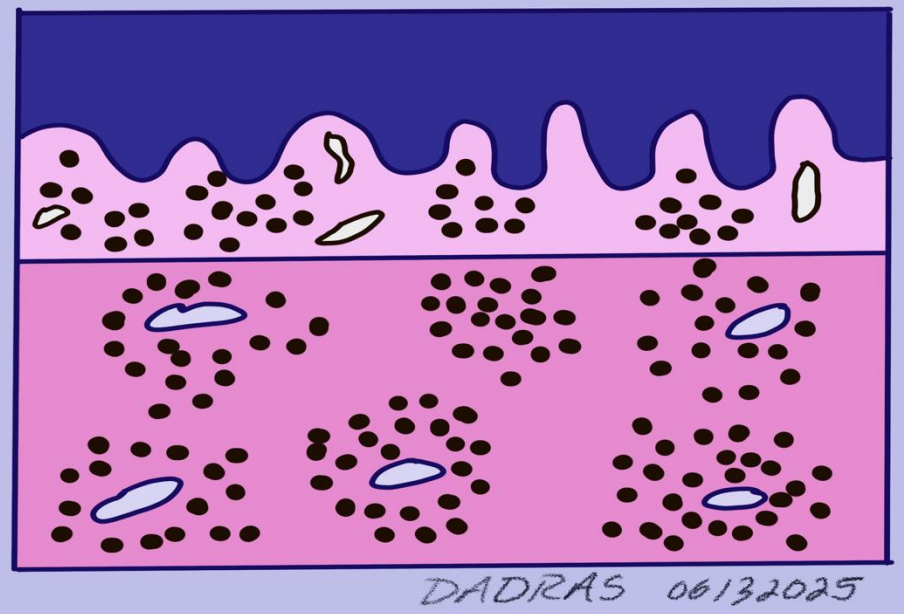
# CUTANEOUS METASTASES



Dermal nodule without epidermal connection

# Introduction: Patterns of Dermal Infiltrate Suggesting Metastasis

Nodular

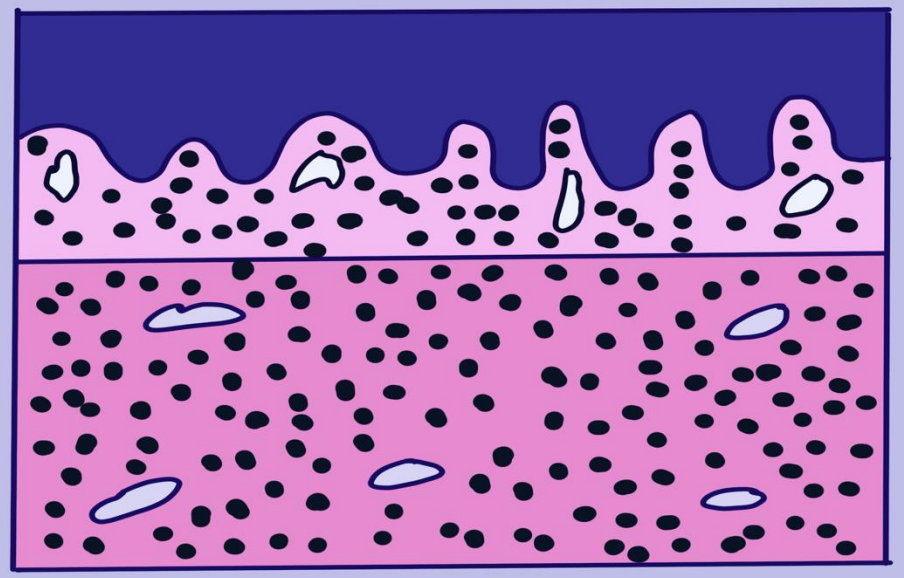



Epidermis

Papillary dermis

Reticular dermis

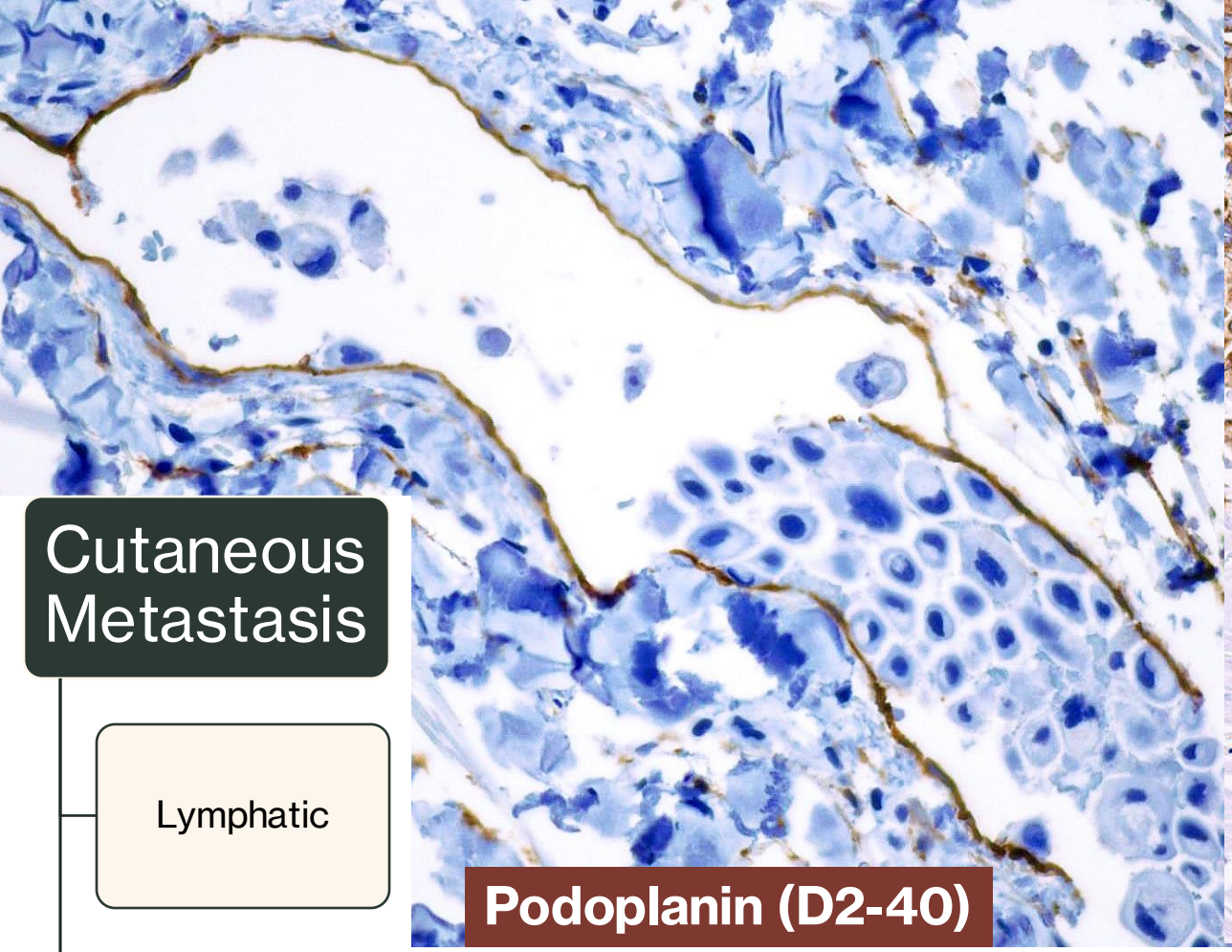
Diffuse

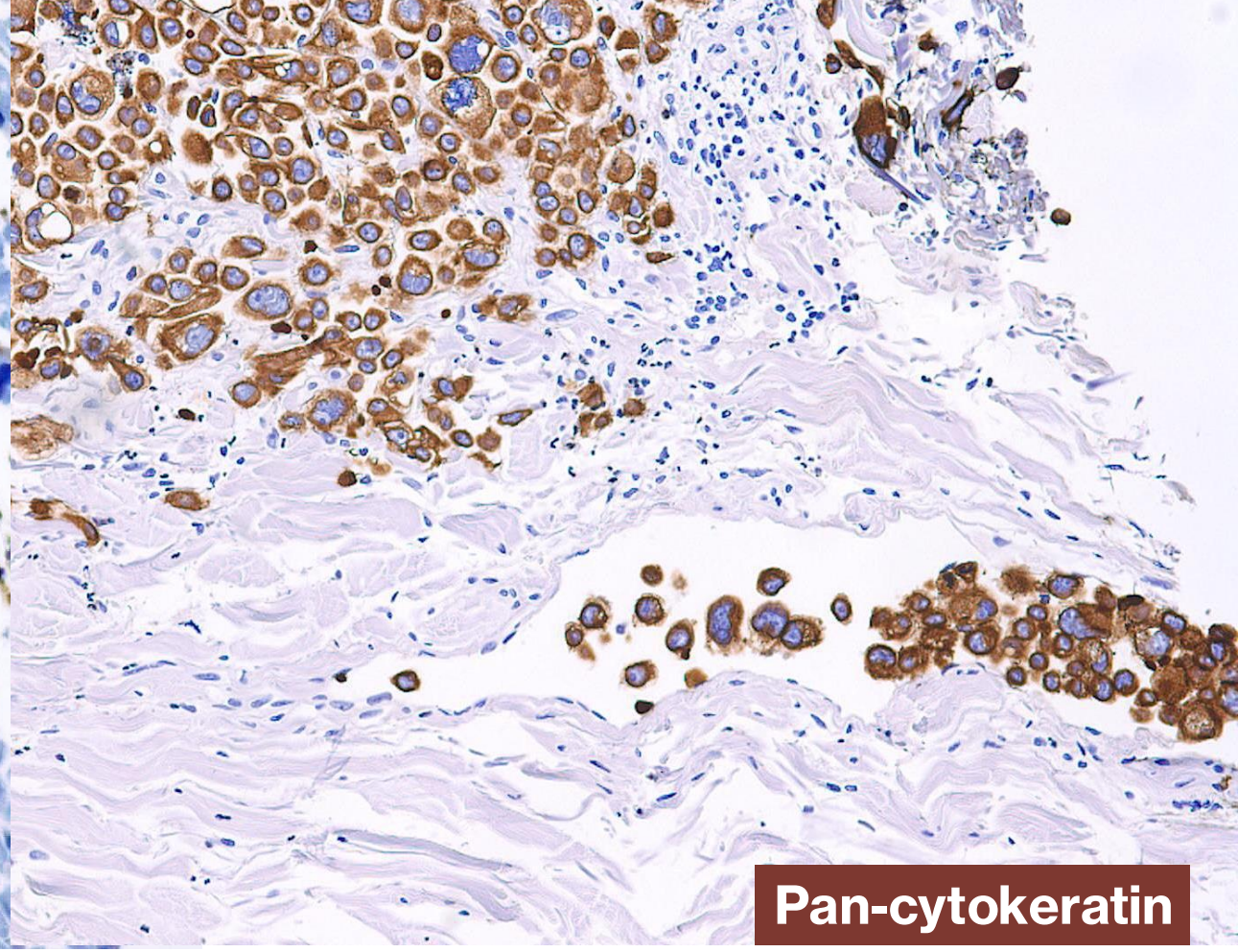


Adnexal carcinoma
Sebaceous carcinoma
Breast ductal carcinoma
Head and neck carcinoma
Thyroid carcinoma
Lung adenocarcinoma
GI adenocarcinoma

GU adenocarcinoma
Merkle cell carcinoma
Squamous cell carcinoma
Basal cell carcinoma
Melanoma
Sarcoma

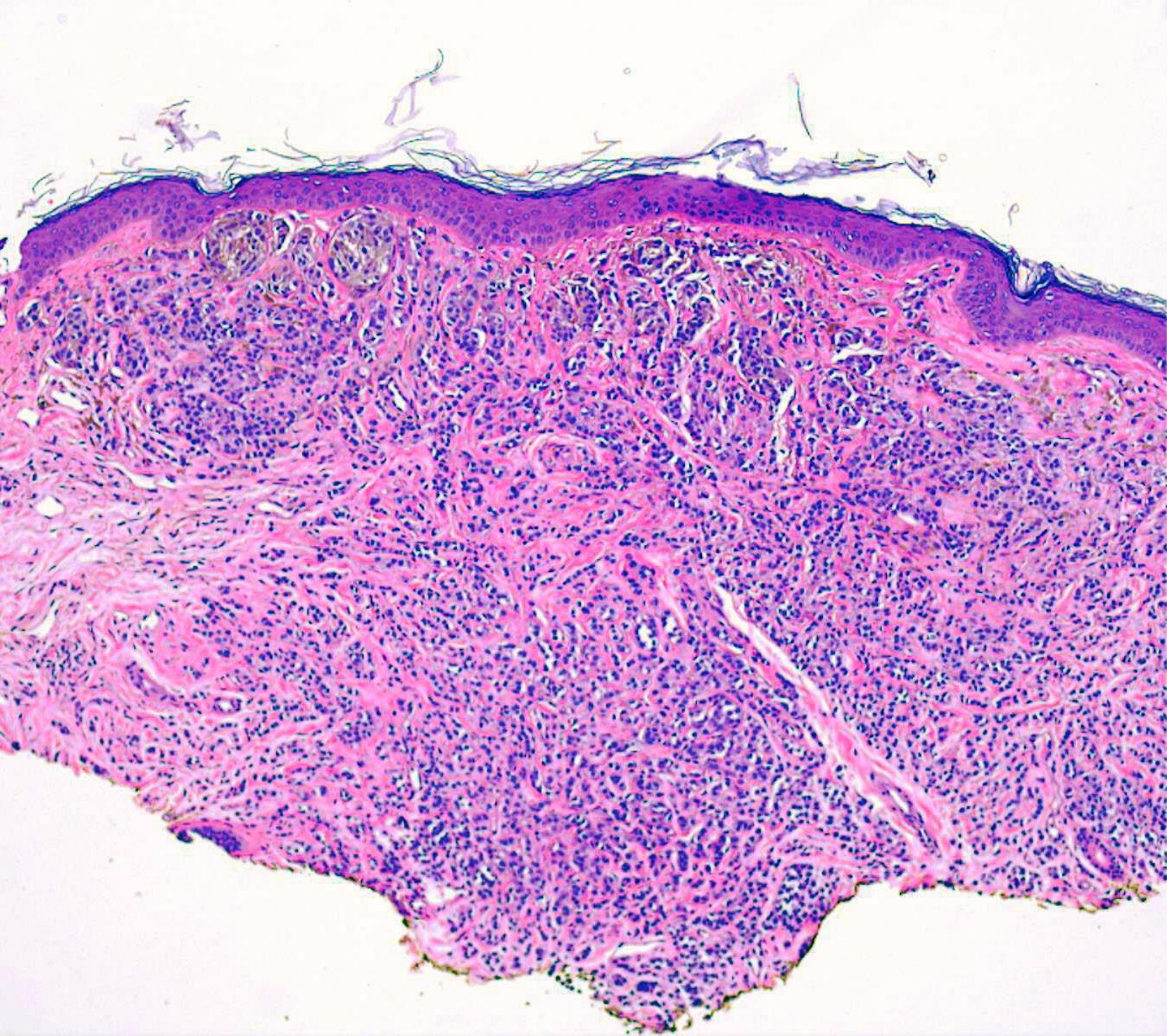
Lymphoma cutis
Leukemia cutis
Mast cell disease




- Cutaneous Metastasis
  - Lymphatic
  - Hematogenous
  - Direct extension

# Metastatic squamous cell carcinoma with lymphatic invasion

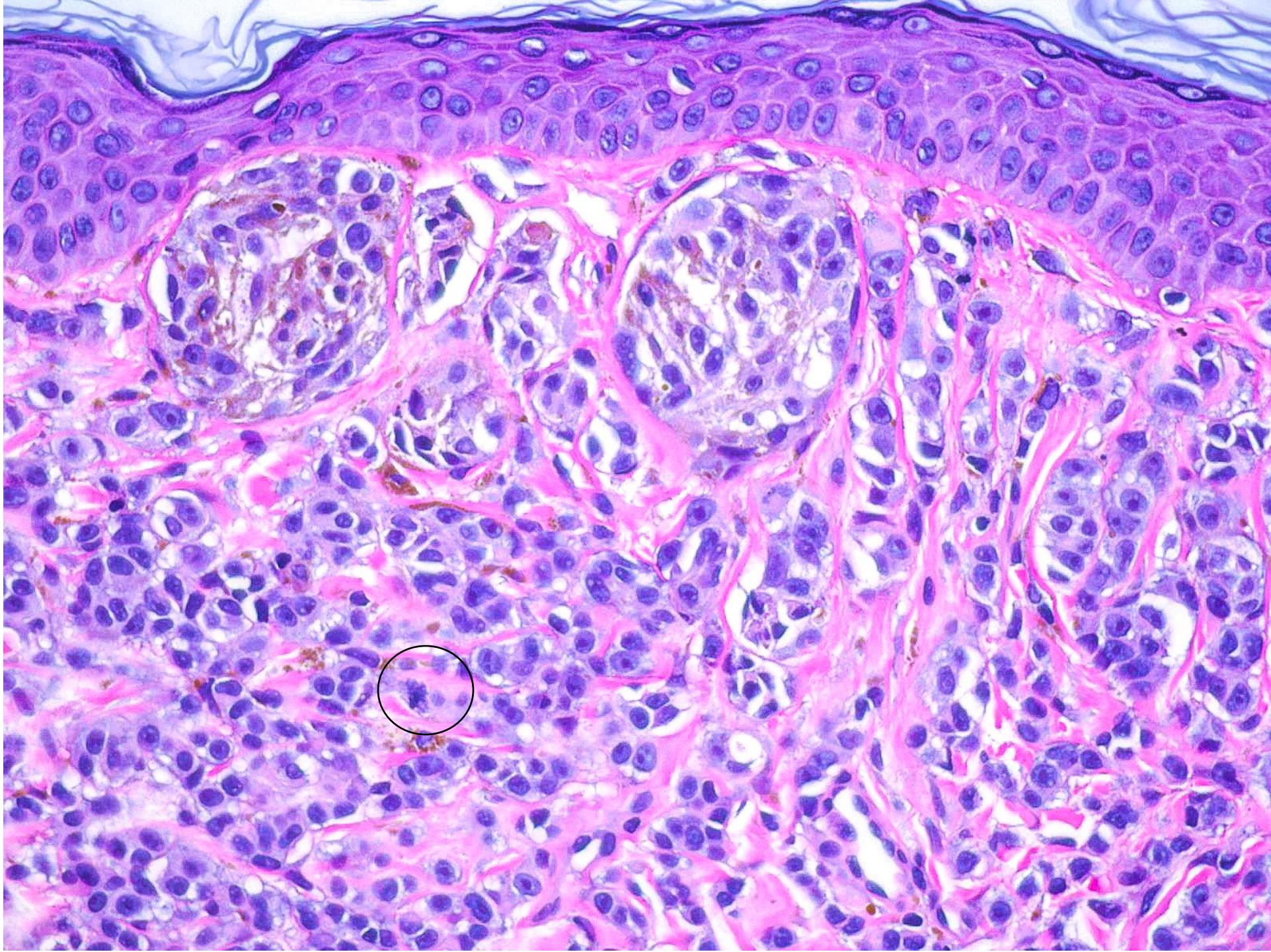


# When to Suspect Metastasis (Not Primary Skin Cancer)

- **Dermal/subcutaneous location** (no epidermal connection and no in-situ component).
- **Unusual cytology** (e.g., single cells, signet-ring cells, clear cells).
- **History of malignancy** (always check!).
- **DDX:**
  - Nevoid melanoma
  - Intradermal nevus

# Metastatic melanoma

- Epidermal thinning/atrophy
- No epidermal connection
- No in-situ component
- Mimics ‘normal’ dermal maturation
- Malignant cytology
- DDX:
  - Nevoid melanoma
  - Intradermal nevus



# Practical Approaches for Unknown Metastasis

- **Clinical history is critical** (known primary, imaging).
- **IHC narrows origin** but requires correlation with morphology.
- **Molecular testing** (e.g., HER2, PD-L1) may guide therapy.
- Clinical investigation is needed

- **First-line Screening:**
  - CK7, CK20, GATA3, TTF-1, PAX8, S100.
- **Breast vs. Lung vs. GI:**
  - GATA3 (breast) vs. TTF-1 (lung) vs. CDX2 (GI).
- **Melanoma vs. Carcinoma:**
  - S100/SOX10+ (melanoma) vs. CK+ (carcinoma).

# Top 5 Skin Metastases: Diagnostic Cheat

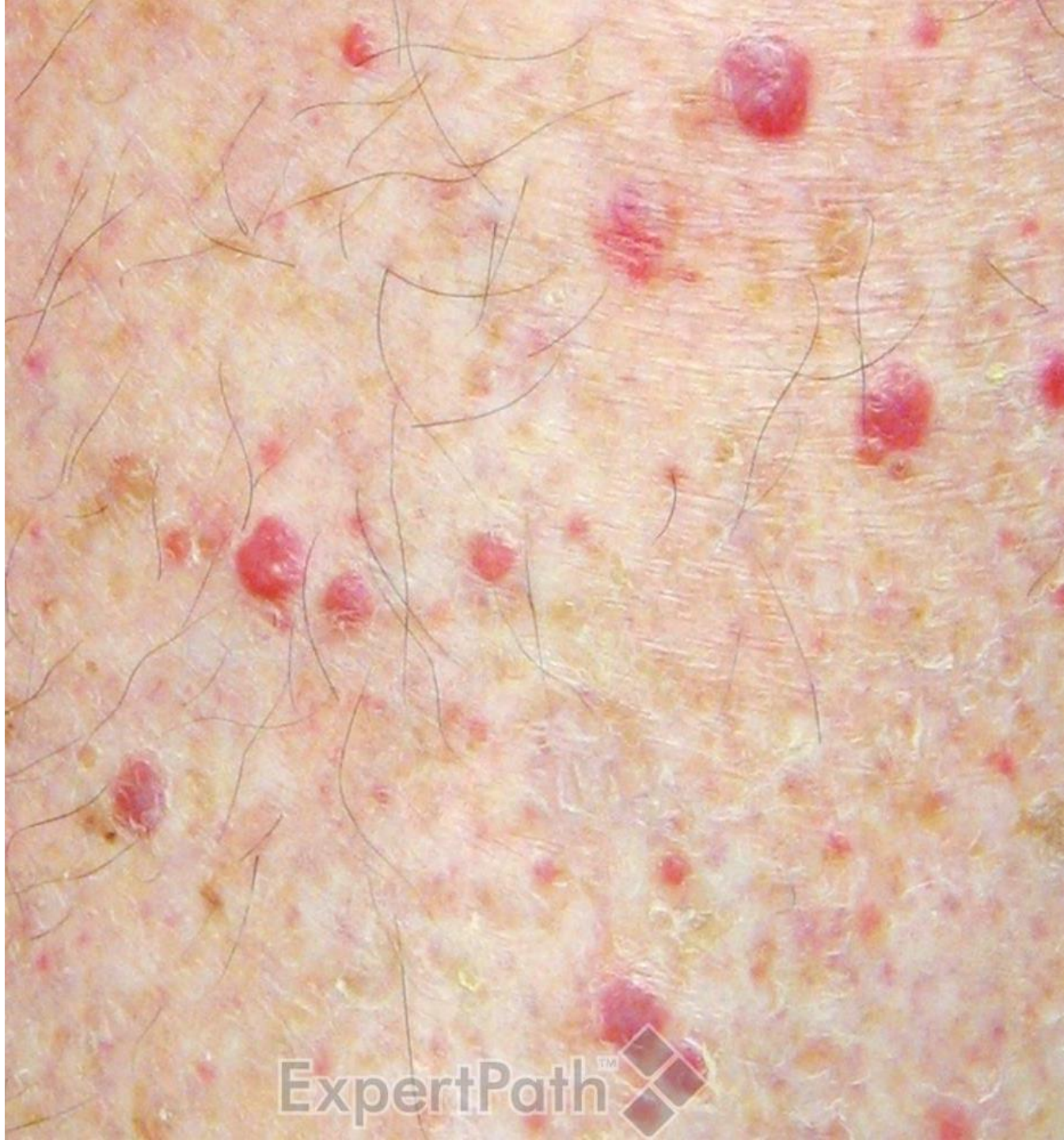
| Cancer Type | Classic Histology | Must-Have IHC Markers | Mimics to Exclude | Clincher for Diagnosis |
|---|---|---|---|---|
| **Breast Carcinoma** | - Ductal: Tubular nests<br>- Lobular: Single-file cells | CK7, GATA3+, ER/PR+, HER2± | Lobular vs. Gastric signet-ring: E-Cadherin- (breast), CK20- | GCDFP-15+ supports breast origin |
| **Melanoma** | - Pagetoid spread<br>- Melanin (if pigmented) | SOX10+, S100+, Melan-A+ | Poorly differentiated carcinoma: CK–, S100+ | PRAME+ in metastases |
| **Lung Adenocarcinoma** | - Glands with mucin<br>- Nuclear grooves | TTF-1+, Napsin A+ | Breast vs. Lung: GATA3–, TTF-1+ | KRAS/EGFR testing for therapy |
| **Colorectal Adenocarcinoma** | - "Dirty necrosis"<br>- Tall columnar cells | CDX2+, CK20+, SATB2+ | Gastric vs. Colorectal: CK7- (colorectal), CK7+ (gastric) | CK7-/CK20+ classic pattern |
| **Renal Cell Carcinoma (Clear Cell)** | - Clear cytoplasm<br>- Vascular stroma | PAX8+, CAIX+, CD10+ | Adrenal vs. Renal: Inhibin- (renal), Melan-A | HGF/c-MET pathway alterations |

# Metastatic Cancers to Skin: Histology & IHC Markers

| Primary Cancer | Histologic Features | Key IHC Markers (+) | Exclusion Markers (–) |
|---|---|---|---|
| **Breast Carcinoma** | - Ductal: Gland formation, desmoplasia<br>- Lobular: Single-file cells, signet-ring forms | GATA3, ER/PR, HER2, GCDFP-15, Mammaglobin, E-Cadherin (lost in lobular) | CK20, TTF-1, PAX8 |
| **Melanoma** | - Epithelioid/spindle cells, pagetoid spread<br>- ± melanin pigment | S100, SOX10, Melan-A, HMB-45, MITF, PRAME | CK7, CK20, EMA |
| **Lung Carcinoma** | - Adenocarcinoma: Glands, mucin<br>- SCC: Keratin pearls<br>- Small cell: "Salt-and-pepper" chromatin | Adeno: TTF-1, Napsin A<br>SCC: p40, CK5/6<br>Small cell: CD56, Synaptophysin, Chromogranin | GATA3, ER, CDX2 |
| **Colorectal Adenocarcinoma** | - "Dirty necrosis," glandular architecture<br>- Signet-ring cells (rare) | CK20+, CDX2+, SATB2+<br>CK7– (usually) | TTF-1, GATA3 |
| **Esophageal Carcinoma** | - SCC: Keratinizing/non-keratinizing nests<br>- Adeno: Intestinal-type glands | SCC: p40, CK5/6<br>Adeno: CK7, CDX2, HER2 | TTF-1, GATA3 |
| **Renal Cell Carcinoma (Clear Cell)** | - Clear cytoplasm, vascular stroma<br>- Tubular/papillary patterns | PAX8, CAIX, RCC, CD10 | CK7, GATA3 |
| **Prostate Adenocarcinoma** | - Small glands, prominent nucleoli<br>- Blue-tinged mucin | PSA, PSAP, NKX3.1, AMACR | GATA3, TTF-1 |
| **Ovarian Carcinoma** | - Papillary/psammoma bodies (serous)<br>- Signet-ring cells (mucinous) | PAX8, WT1, CA125, CK7 | TTF-1, CDX2 |
| **Gastric Adenocarcinoma** | - Glands/signet-ring cells<br>- Mucinous or intestinal-type | CK7, CDX2, HER2 | TTF-1, GATA3 |
| **Urothelial Carcinoma** | - Nested/papillary architecture<br>- Eosinophilic cytoplasm | GATA3, CK7, CK20, p63 | ER, TTF-1 |

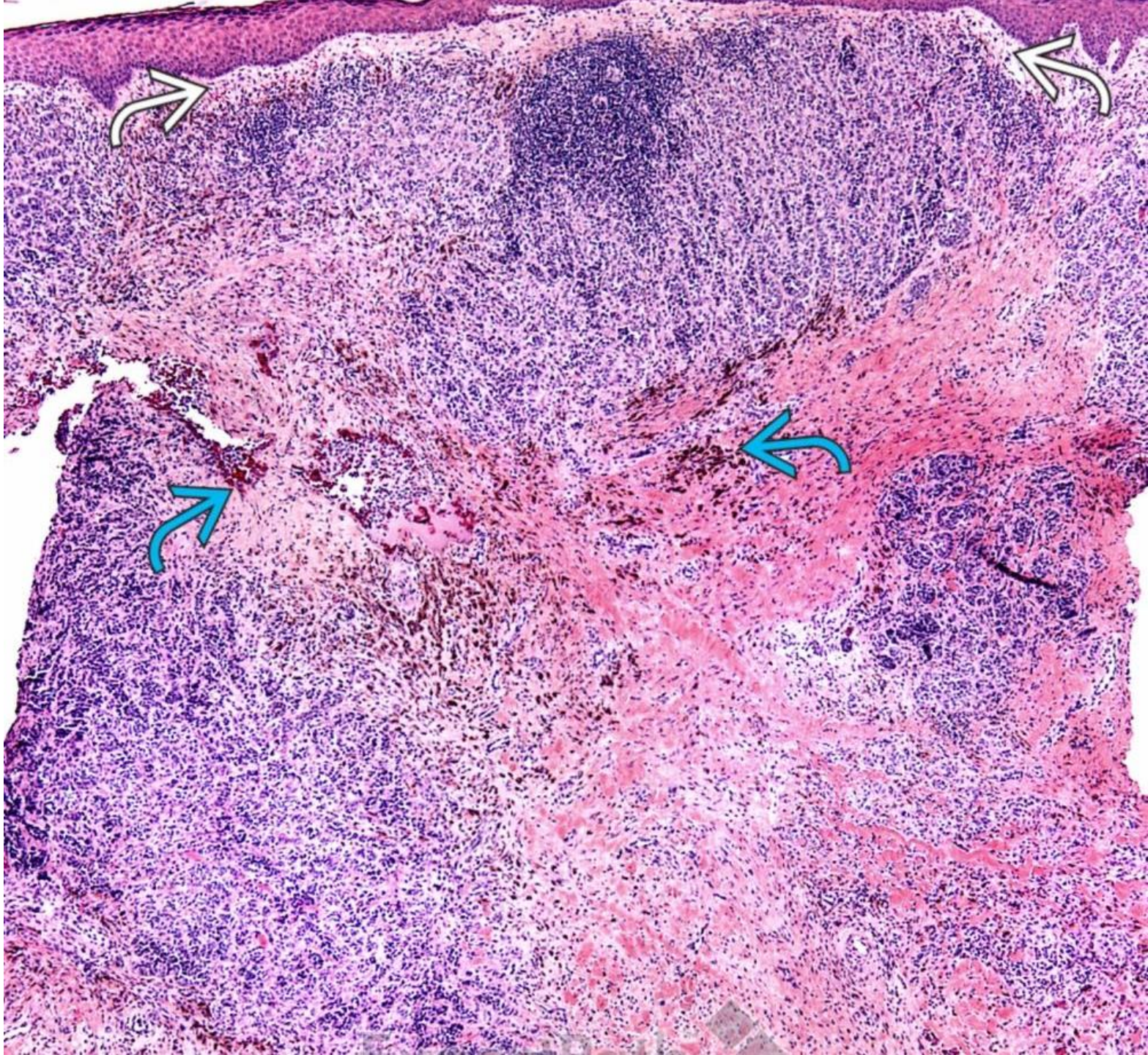
# Metastatic melanoma

- It can present with pink lesions, as in this case, in which the patient had numerous pink papules on the leg. (Courtesy Yale Dermatology Residents' Slide Collection.)



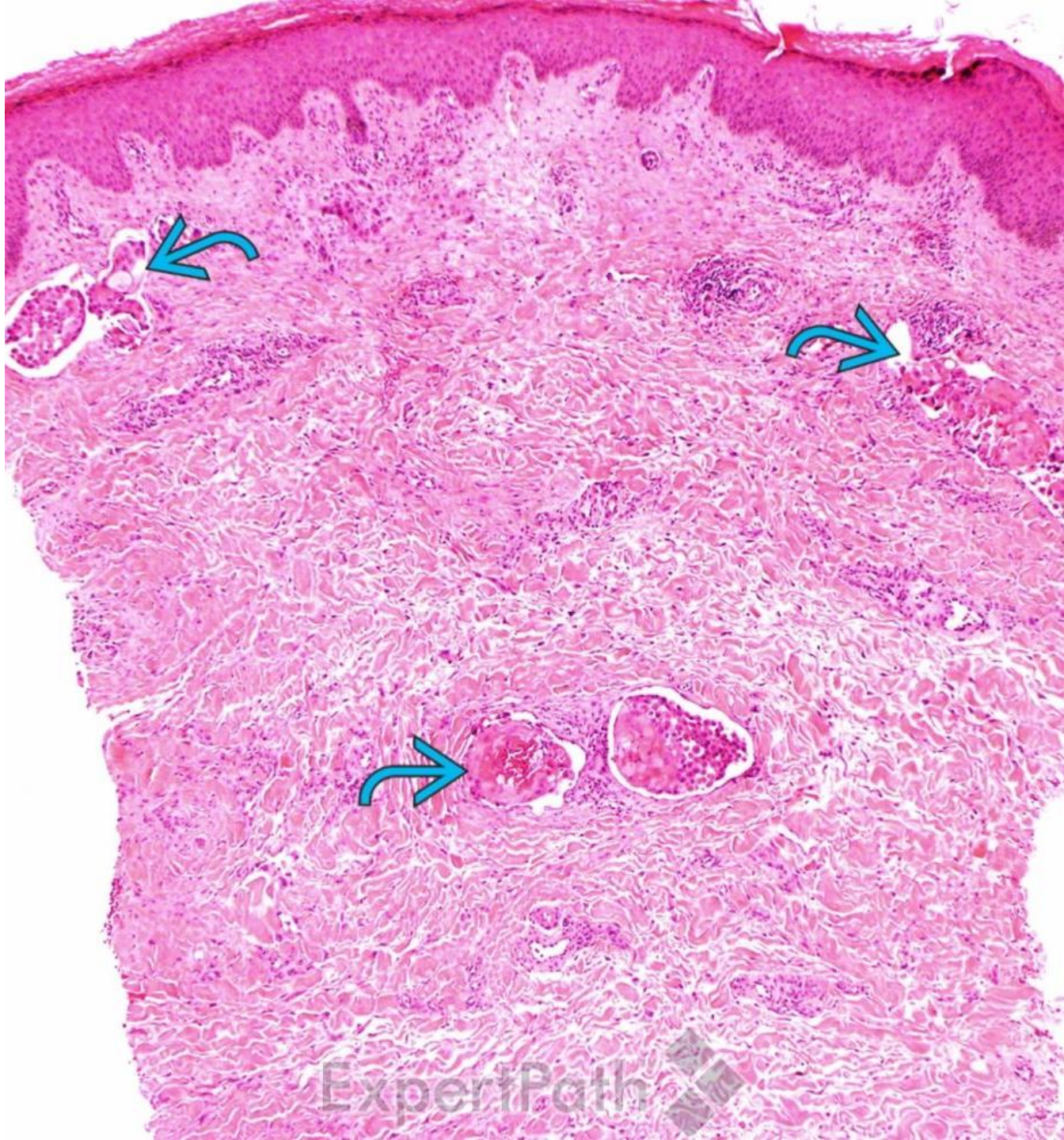
# Metastatic melanoma

- This shows extensive involvement of the dermis with prominent areas of pigmentation seen (cyan curved arrow). There is a thin grenz zone (white curved arrow) present and no evidence of epidermotropism identified.



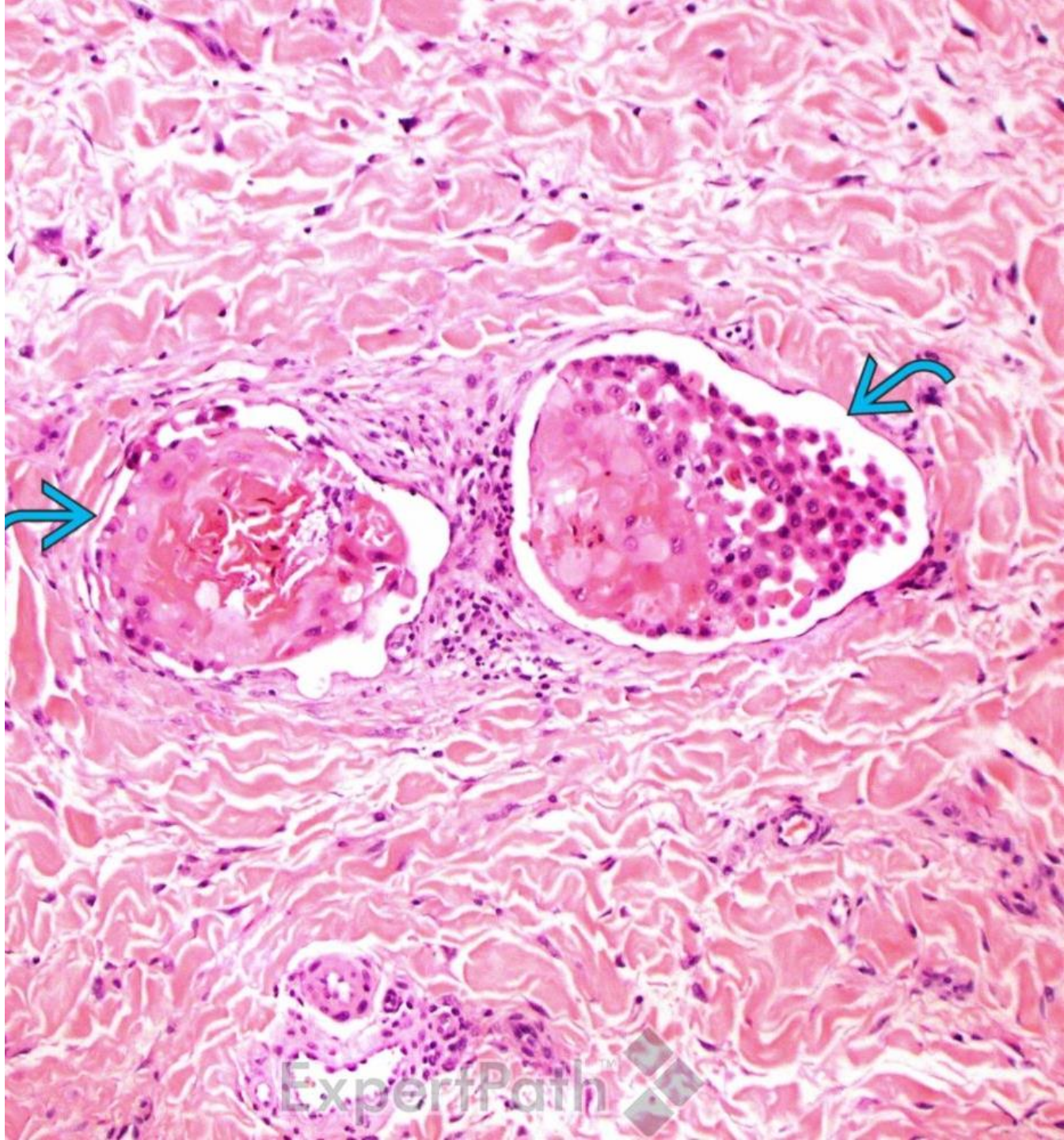
# Metastatic cutaneous squamous cell carcinoma

- This is an example to the skin involving multiple superficial and deep dermal lymphatics (cyan curved arrow). The patient had a history of multiple cutaneous squamous cell carcinomas but no internal organ malignancies.



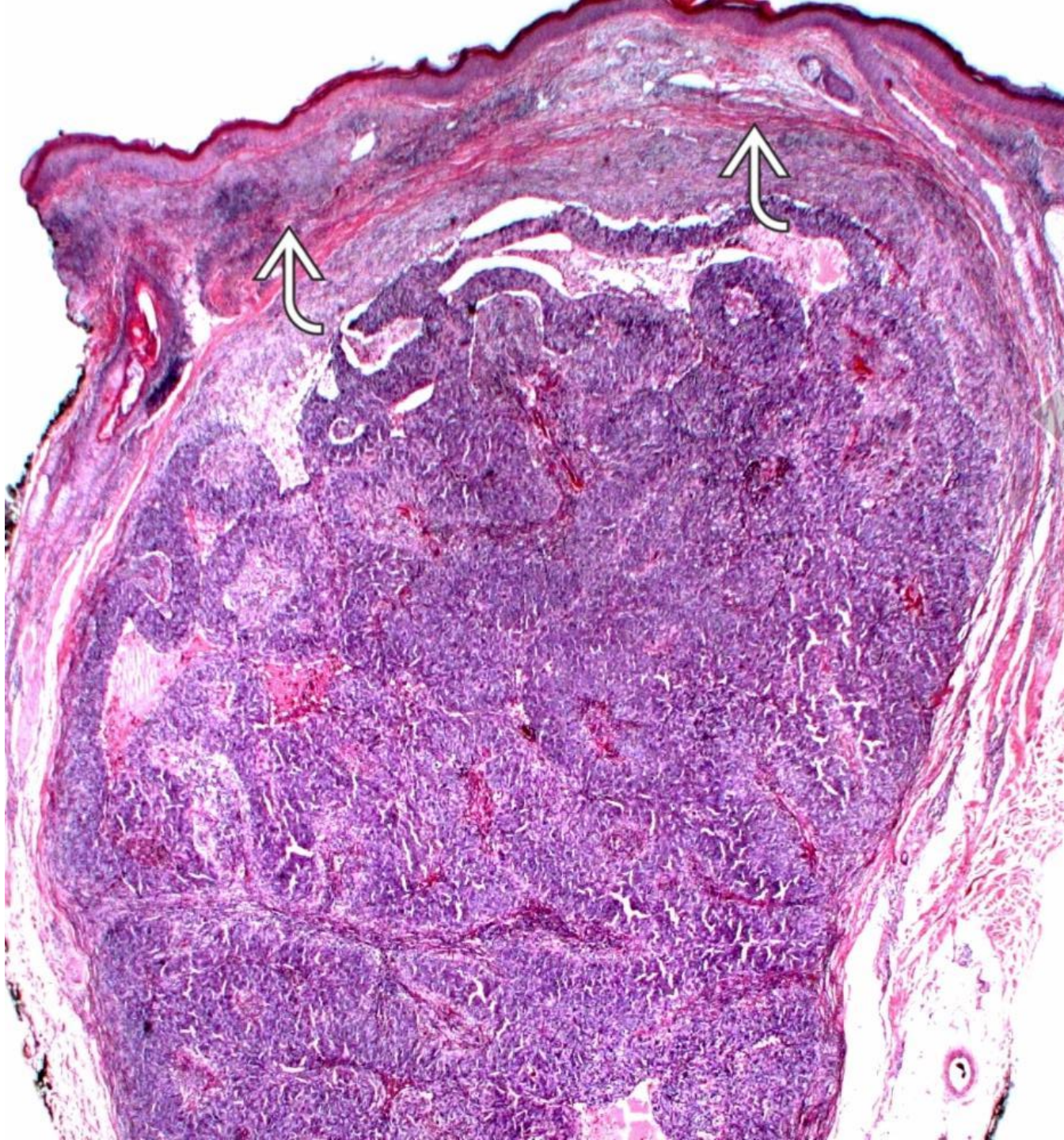
# Metastatic cutaneous squamous cell carcinoma

- Higher magnification, metastasis to the skin involving the dermal lymphatics (cyan curved arrow).



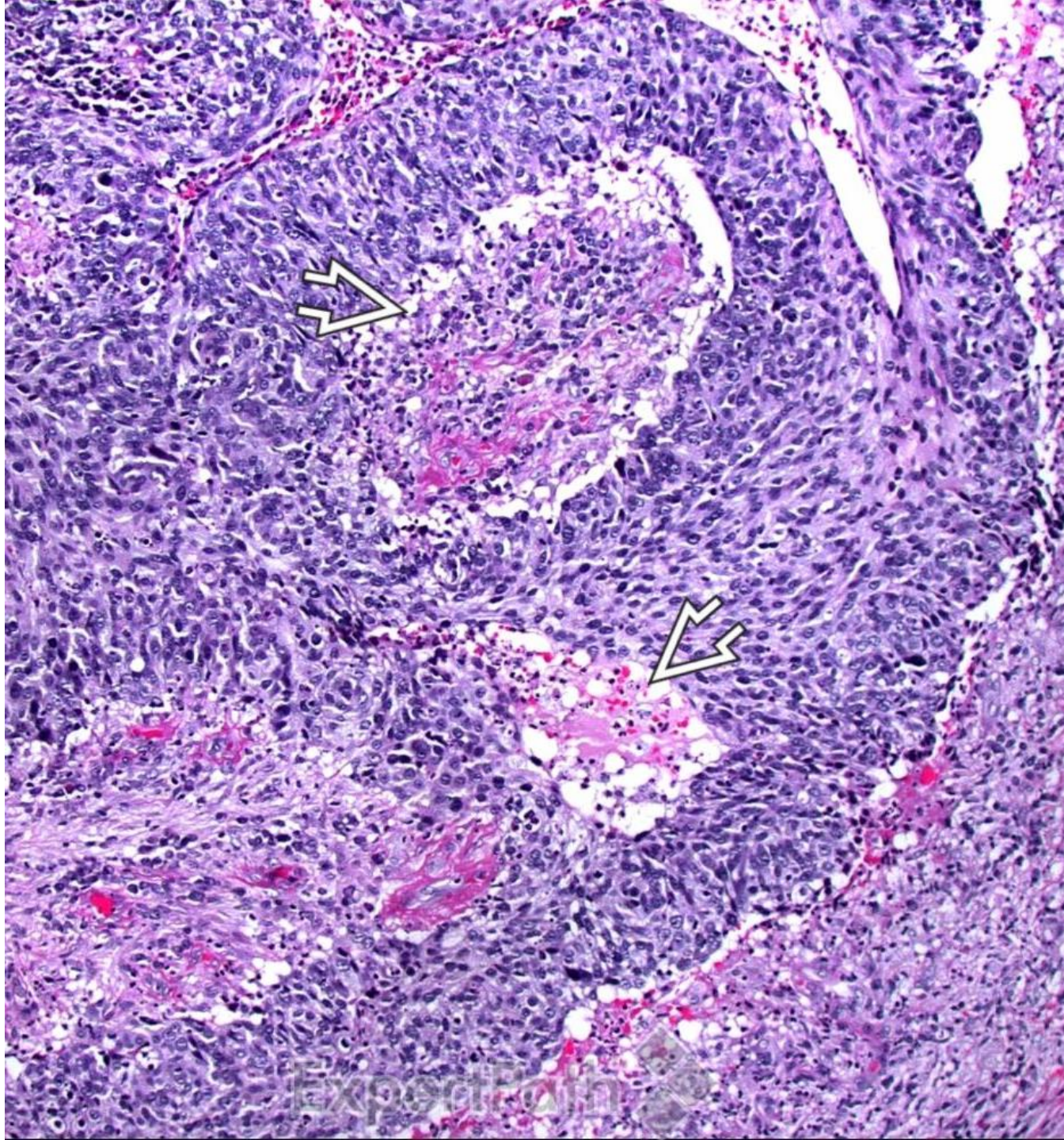
# Metastatic sebaceous carcinoma

- This is an example of metastasis to the cheek of an elderly patient (who had a primary diagnosed on the eyelid several years prior). The tumor forms a large, expansile nodule in the deep dermis but spares the papillary dermis (white curved arrow) and epidermis.



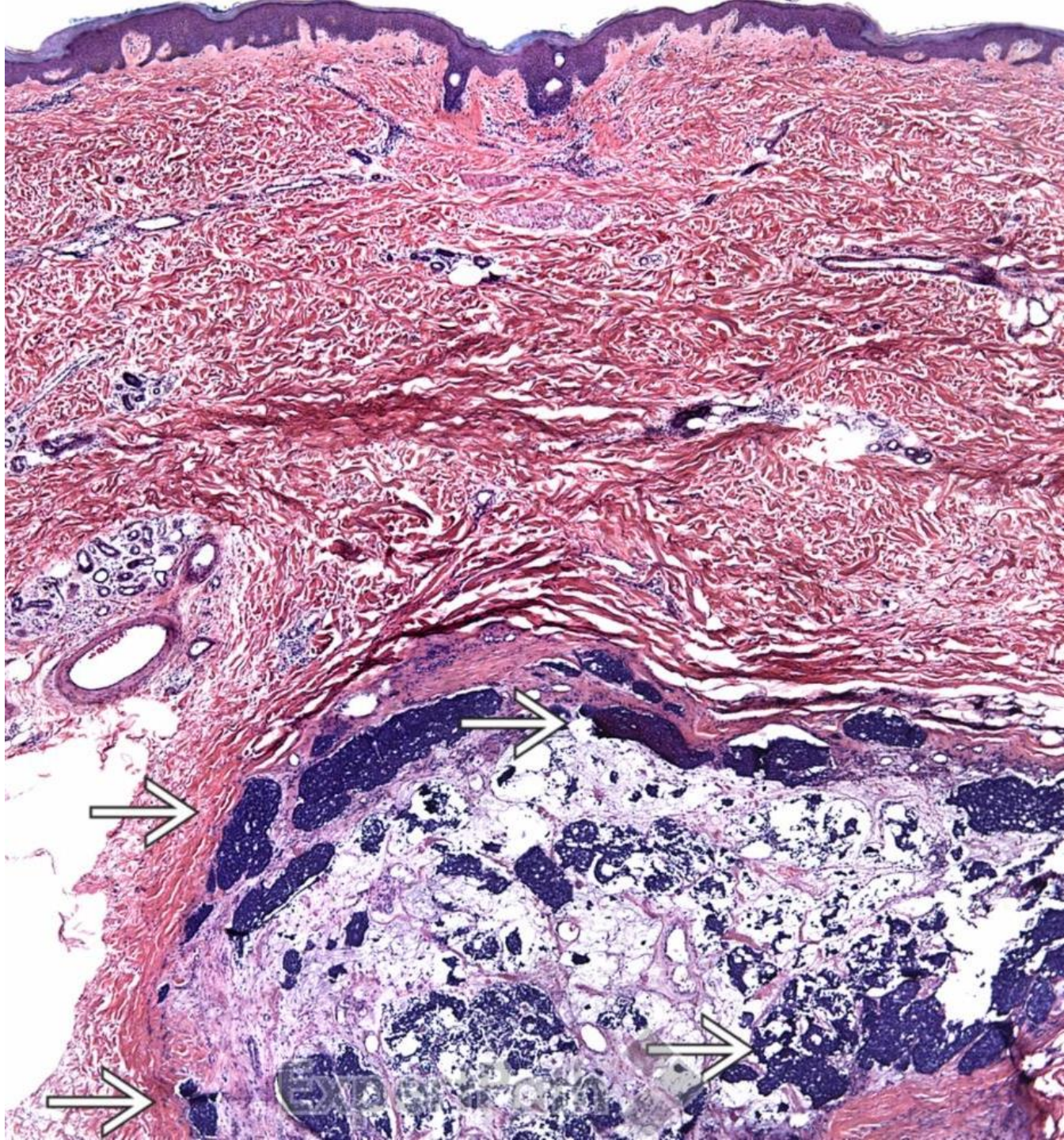
# Metastatic sebaceous carcinoma

- Higher magnification shows the large, pleomorphic tumor cells (white open arrow) forming cellular lobules surrounding central collections of inflammatory cells, serum, and comedonecrosis.

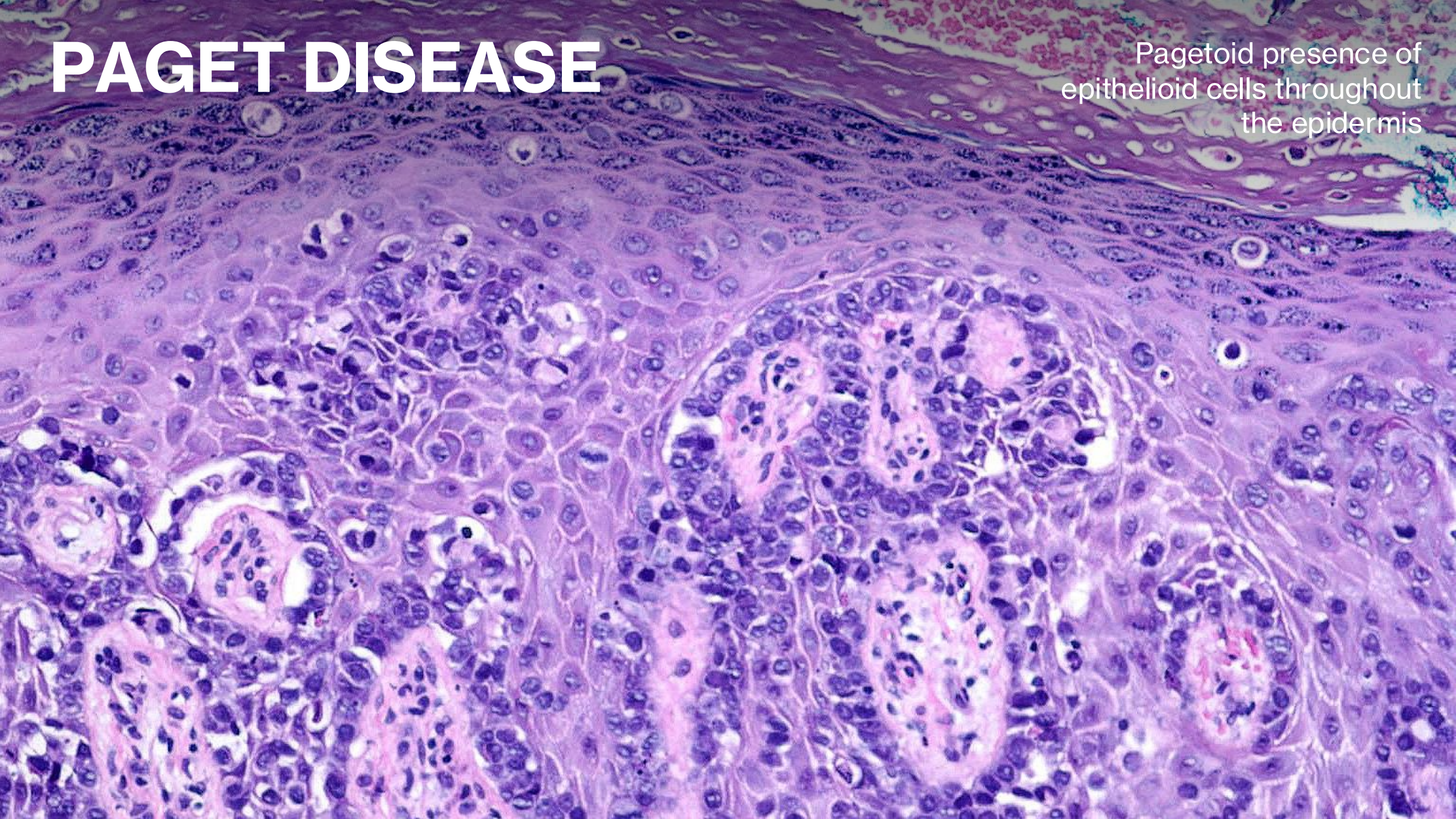


# Metastatic Merkel cell carcinoma

- Other primary skin tumors can also metastasize to the skin. There are islands (white solid arrow) composed of small, dark blue cells in the deep dermis.



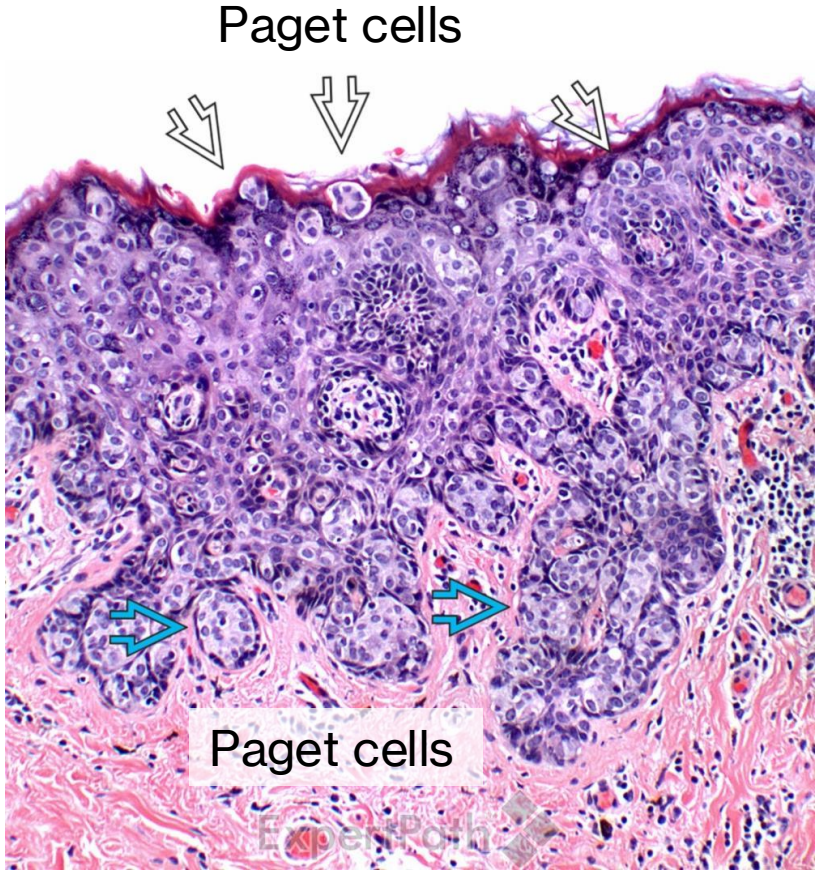
# PAGET DISEASE

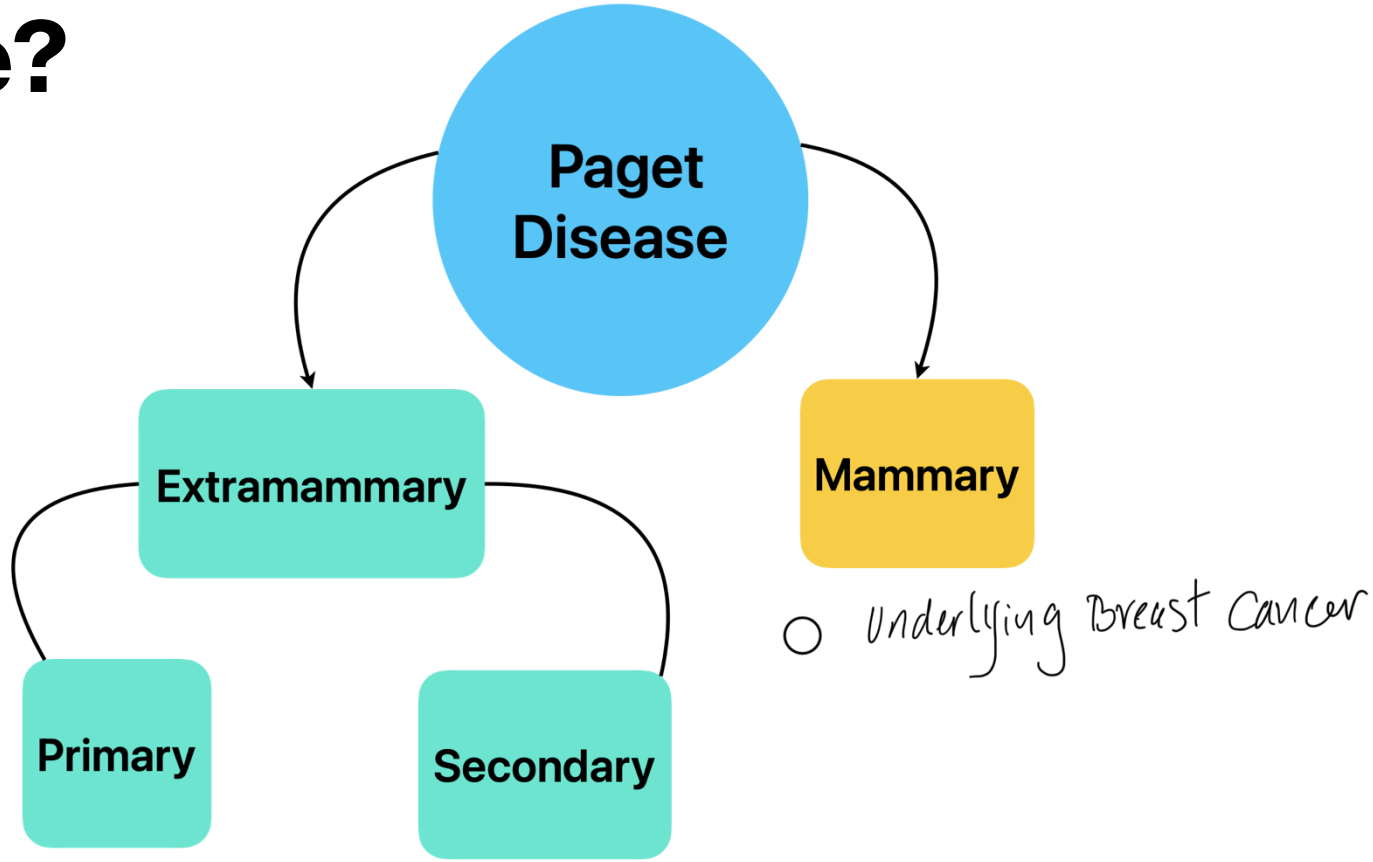


Pagetoid presence of epithelioid cells throughout the epidermis

# What is Paget disease?

Similar histopathology, different disease entities

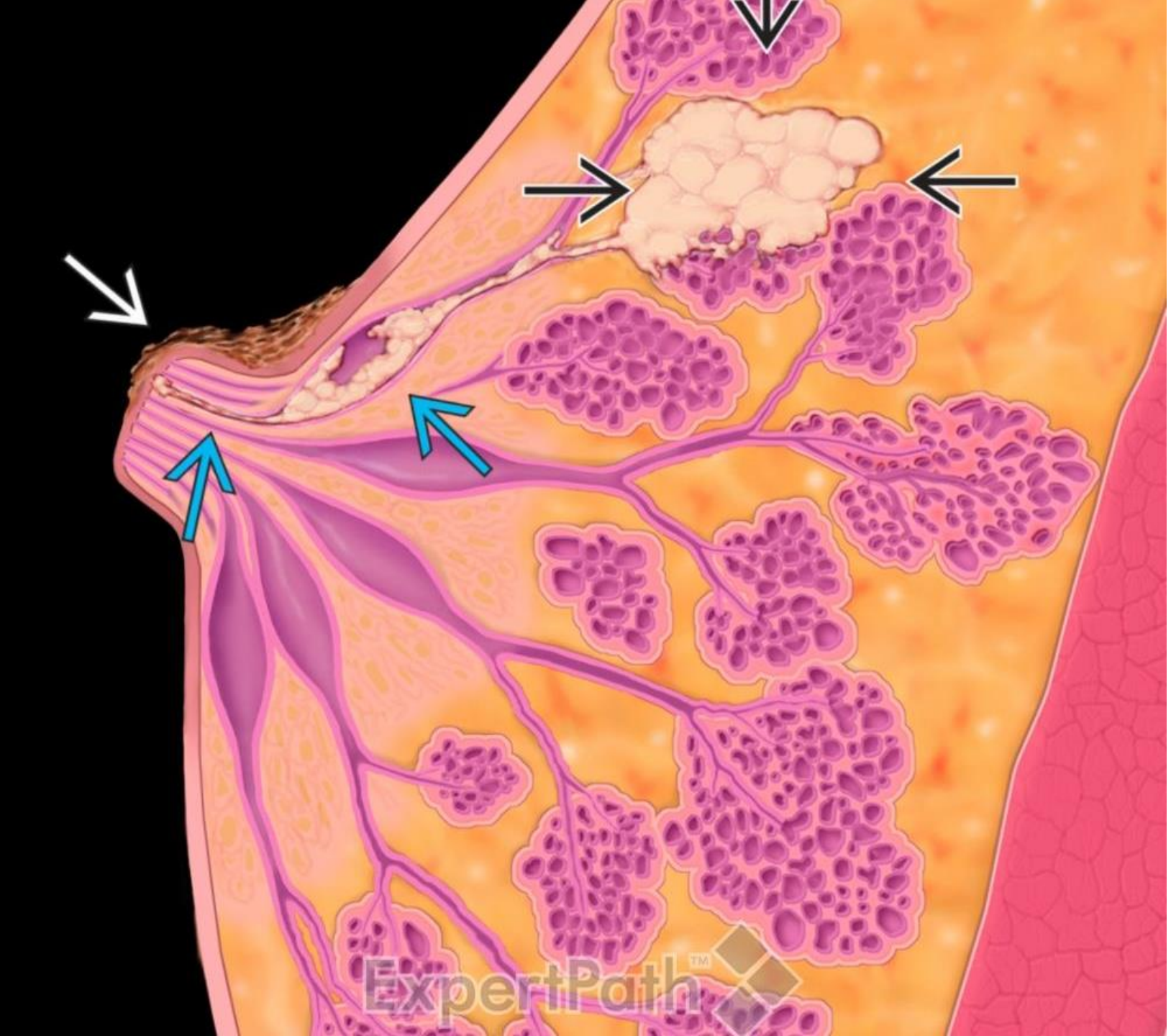



- Underlying Breast Cancer
- Arises from apocrine cells or Toker cells
- Not associated with other cancers
- Nearby carcinoma invades the skin

# Clinical Features of Paget Disease: Mammary vs. Extramammary

| Feature | Mammary Paget Disease (MPD) | Extramammary Paget Disease (EMPD) |
|---|---|---|
| **Location** | Nipple/areola (unilateral) | Vulva, perianal, scrotum, axilla, penis (extramammary sites) |
| **Association** | Underlying breast carcinoma (DCIS or invasive) in >90% | Underlying malignancy in ~25-30% (e.g., rectal, urothelial, or adnexal carcinoma) |
| **Appearance** | Erythematous, scaly, crusted, eczematous plaque | Similar eczematous/psoriasiform plaque, may be moist or ulcerated |
| **Symptoms** | Itching, burning, nipple discharge | Pruritus, pain, bleeding |



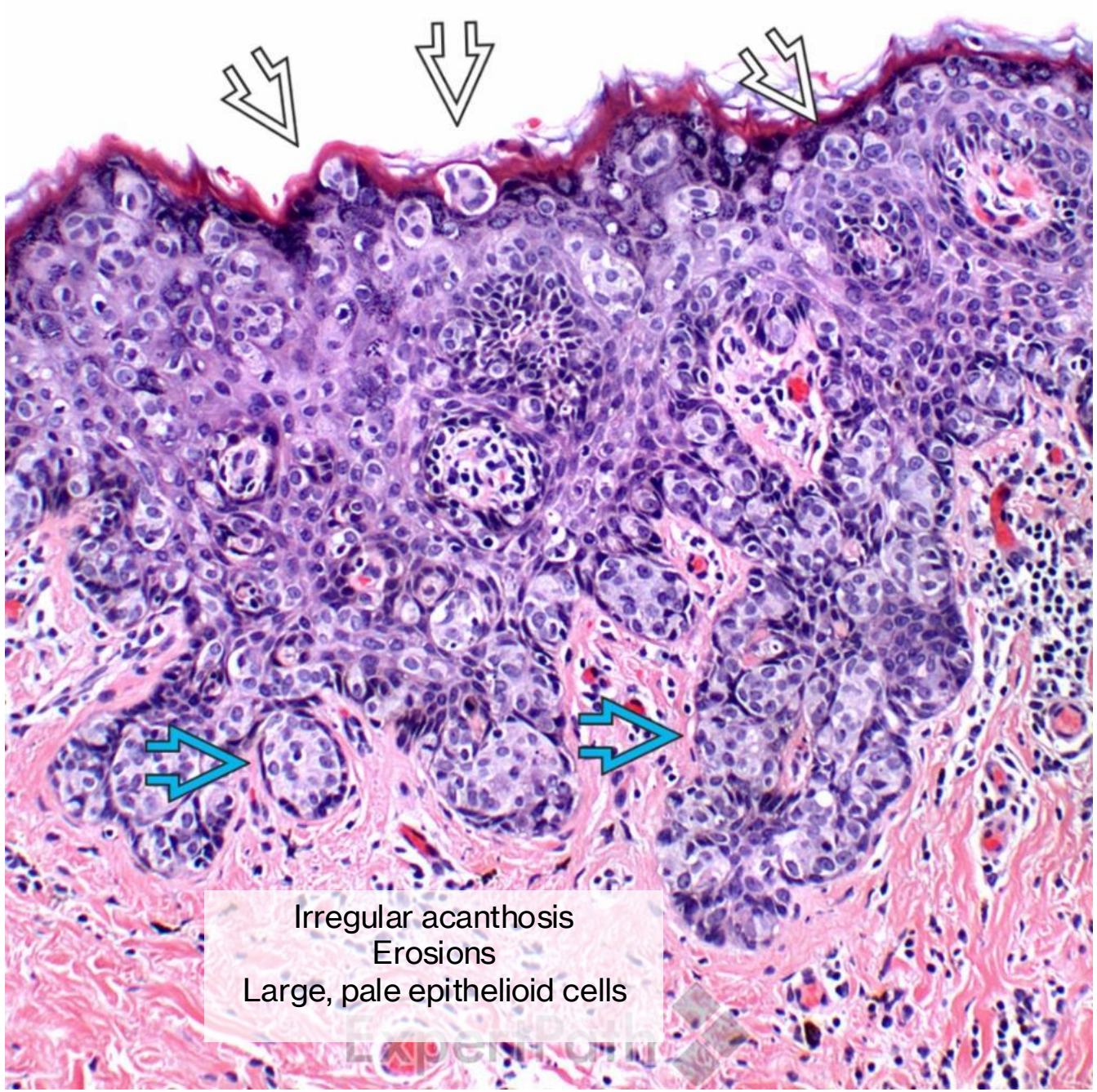

# What is Mammary Paget Disease?

Invasive carcinoma (black solid arrow) is present deeper in the breast. The cells from the associated DCIS can grow into the lactiferous sinuses (cyan solid arrow) and onto the nipple skin (white solid arrow).

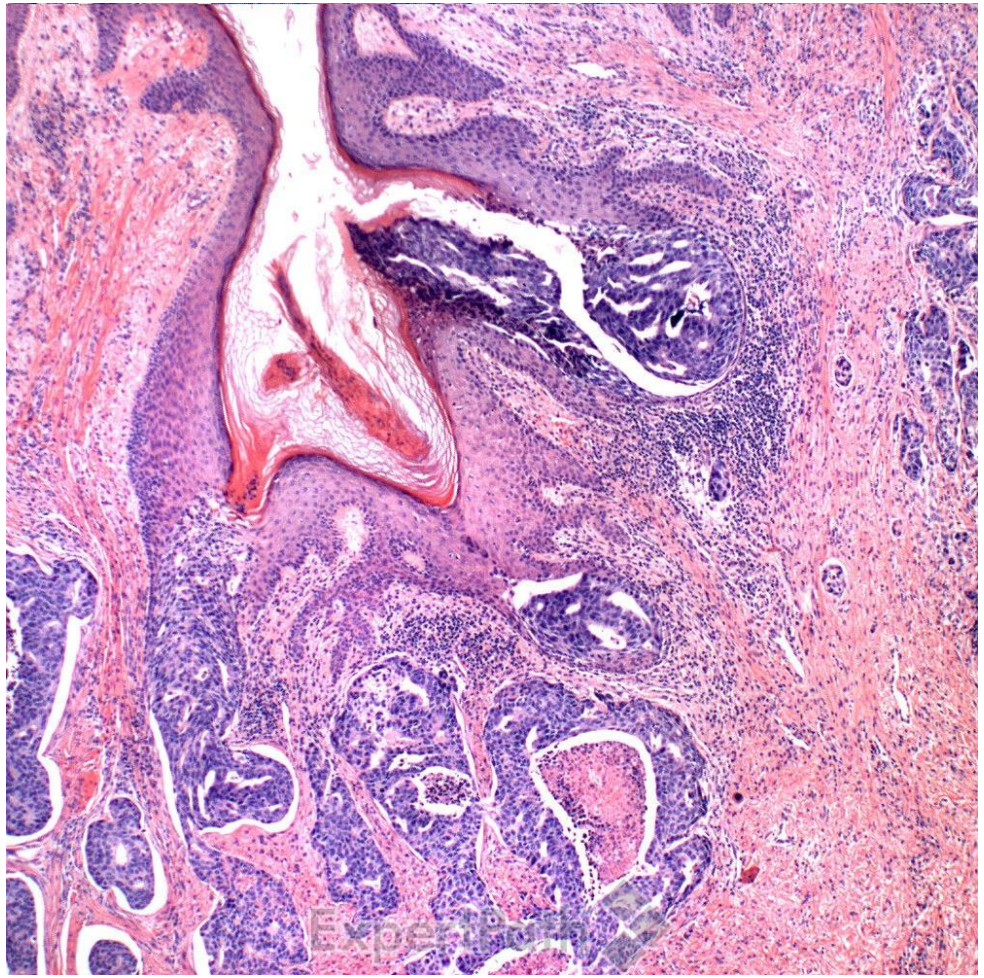
# Histologic Features of Paget Disease: Mammary vs. Extramammary

| Feature | Mammary Paget Disease (MPD) | Extramammary Paget Disease (EMPD) |
|---|---|---|
| **Paget Cells** | Large, round, pale-staining cells with prominent nuclei | Similar morphology but may show more glandular differentiation |
| **Location** | Epidermis (single cells or clusters) | Epidermis, often extends into adnexal structures |
| **Stroma** | Underlying dermal invasion suggests carcinoma | May show dermal invasion if associated malignancy |

# Mammary Paget disease (MPD)

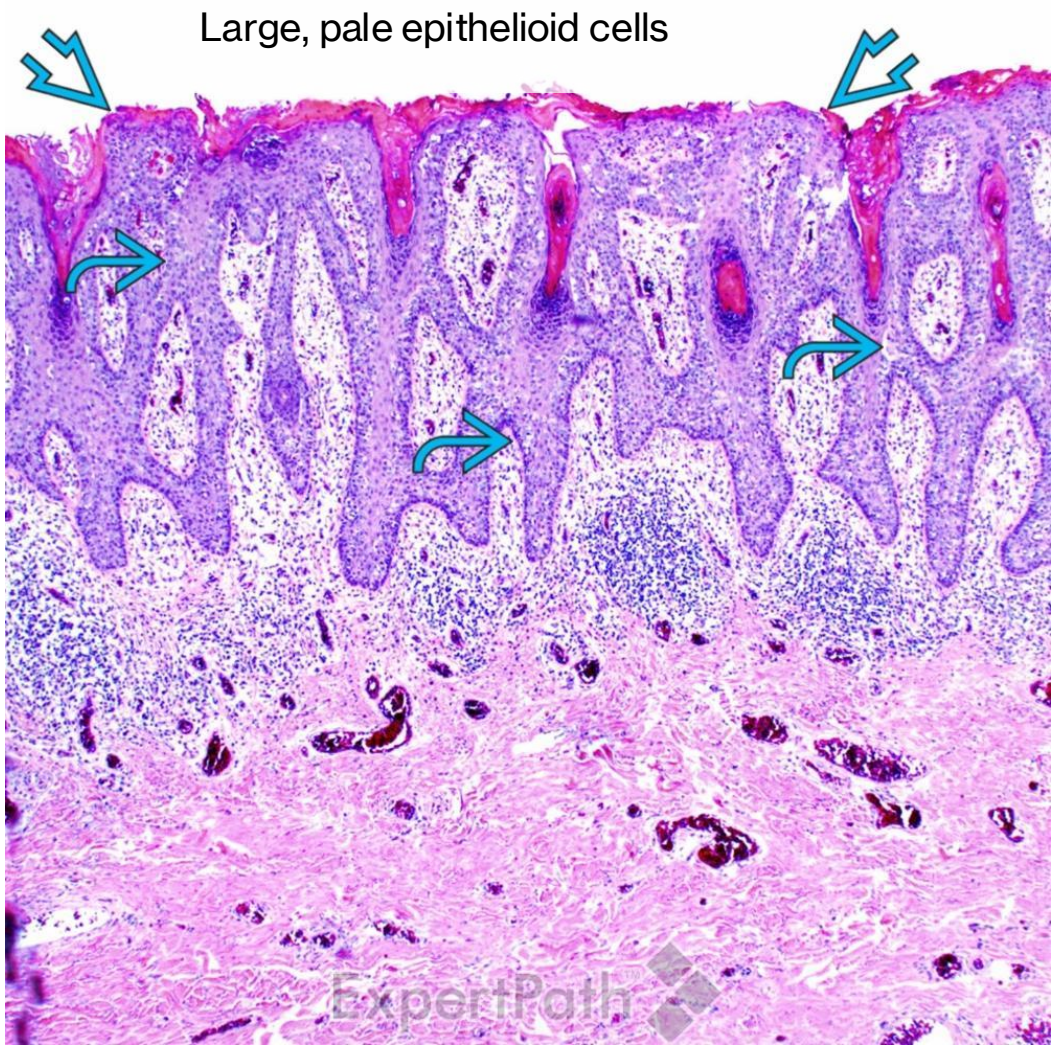



Invasive carcinoma invades the epidermis

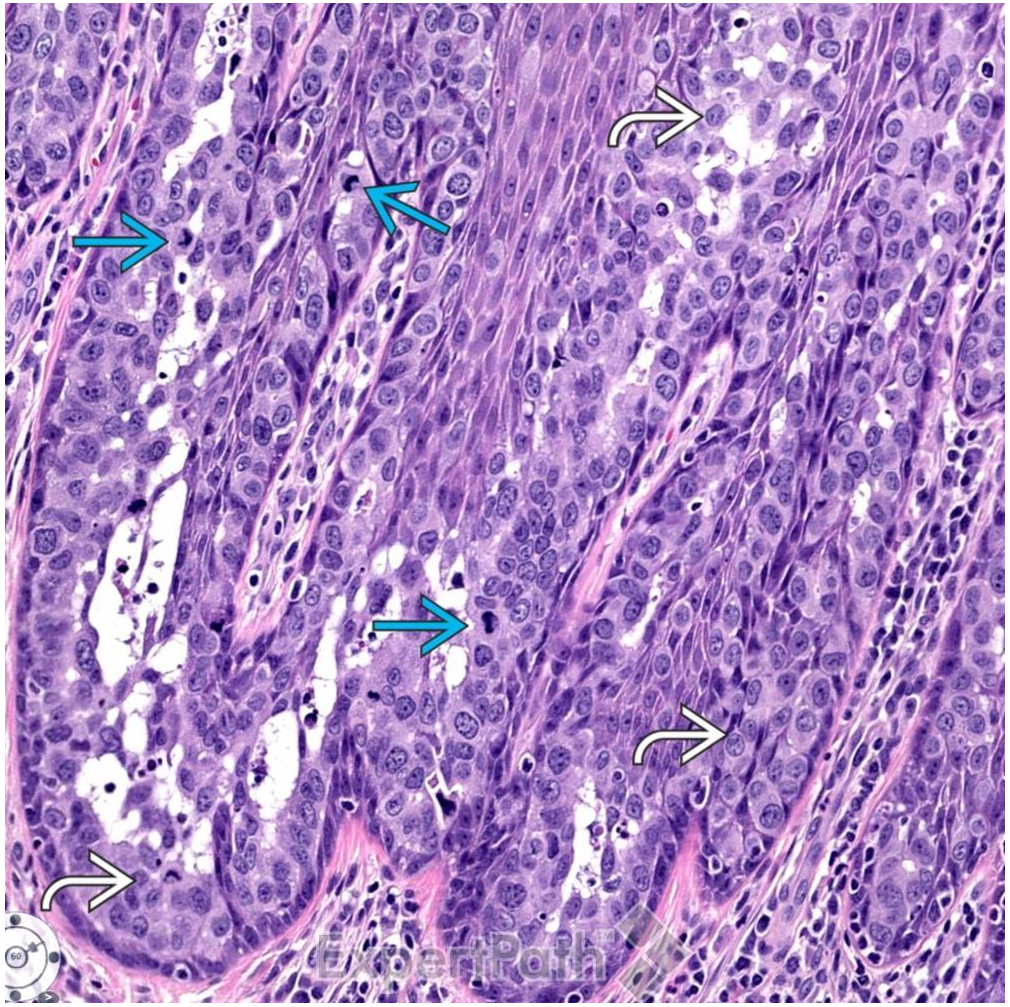


# Primary cutaneous extramammary Paget disease (EMPD)

Irregular acanthosis
Erosions
Large, pale epithelioid cells




Enlarged, atypical epithelioid pagetoid cells
Glandular spaces
Scattered mitoses



# Histological differential diagnosis for Paget disease

| Differential Diagnosis | Histologic Clues | Key IHC Markers |
|---|---|---|
| **1. Paget Disease (MPD/EMPD)** | - Large, round, pale **Paget cells** with prominent nuclei<br>- **Intraepidermal singly or in clusters**<br>- ± mucin vacuoles (PAS+/D-PAS+) | **MPD:** CK7+, HER2+, GCDFP-15+, ER/PR+ (if breast origin)<br>**EMPD:** CK7+, CK20±, AR+ (vulvar), HER2- (usually) |
| **2. Pagetoid Melanoma (In-Situ or Invasive)** | - **Pagetoid melanocytes** with dusty cytoplasm<br>- **Junctional nesting** (unlike Paget)<br>- ± melanin pigment | **S100+, SOX10+, Melan-A+, HMB45+**<br>**CK7–, HER2–** |
| **3. Bowen's Disease (SCC in situ)** | - **Full-thickness keratinocyte atypia**<br>- Dyskeratotic cells<br>- No mucin vacuoles | **p40+, p63+, CK5/6+**<br>**CK7–, HER2–** |
| **4. Toker Cells (Nipple)** | - **Small, bland clear cells** in nipple epidermis<br>- No atypia/mitoses | **CK7+, ER+**<br>**HER2–, GCDFP-15–** |
| **5. Pagetoid Reticulosis (Mycosis Fungoides Variant)** | - **Epidermotropic lymphocytes** with cerebriform nuclei<br>- No mucin | **CD3+, CD4+, CD8±**<br>**CK7–** |
| **6. Sebaceous Carcinoma (Pagetoid Spread)** | - **Foamy/vacuolated cytoplasm** (lipid-rich)<br>- Central nuclear indentation | **EMA+, Adipophilin+**<br>**CK7–, HER2–** |
| **7. Merkel Cell Carcinoma (Epidermotropic)** | - **Small blue cells** with scant cytoplasm<br>- Salt-and-pepper chromatin | **CK20+ (dot-like), Synaptophysin+**<br>**CK7–** |
| **8. Extramammary Pagetoid Spread from Internal CA** (e.g., rectal, bladder) | - **Morphologically identical to EMPD**<br>- History of primary malignancy | **CK20+ (if rectal/urothelial)**<br>**CDX2+ (GI)** |

# Immunohistochemical (IHC) Markers

| Marker | Mammary Paget Disease (MPD) | Extramammary Paget Disease (EMPD) |
|---|---|---|
| CK7 | Positive (strong, diffuse) | Positive (most cases) |
| **CK20** | Usually negative (unless GI/urologic origin) | Positive in ~50% (if associated with rectal/urothelial Ca) |
| **GCDFP-15** | Positive (supports mammary origin) | Variable (often negative) |
| HER2/neu | Often positive (if associated with HER2+ breast cancer) | Rarely positive (unless secondary to breast metastasis) |
| ER/PR | Positive if ER/PR+ breast cancer | Usually negative |
| MUC1 | Positive | Positive |
| PAS/D-PAS | Positive (mucin-secreting cells) | Positive (if mucin-producing) |
| CEA | Positive (cytoplasmic) | Positive (cytoplasmic) |
| AR (Androgen Receptor) | Negative (unless male breast cancer) | Often positive (especially in vulvar/perianal cases) |
| P63 | Negative (helps exclude squamous or myoepithelial origin) | Negative (unless squamous differentiation) |

# Summary: Paget Disease

**MPD** is almost always linked to breast cancer → treat the underlying malignancy.

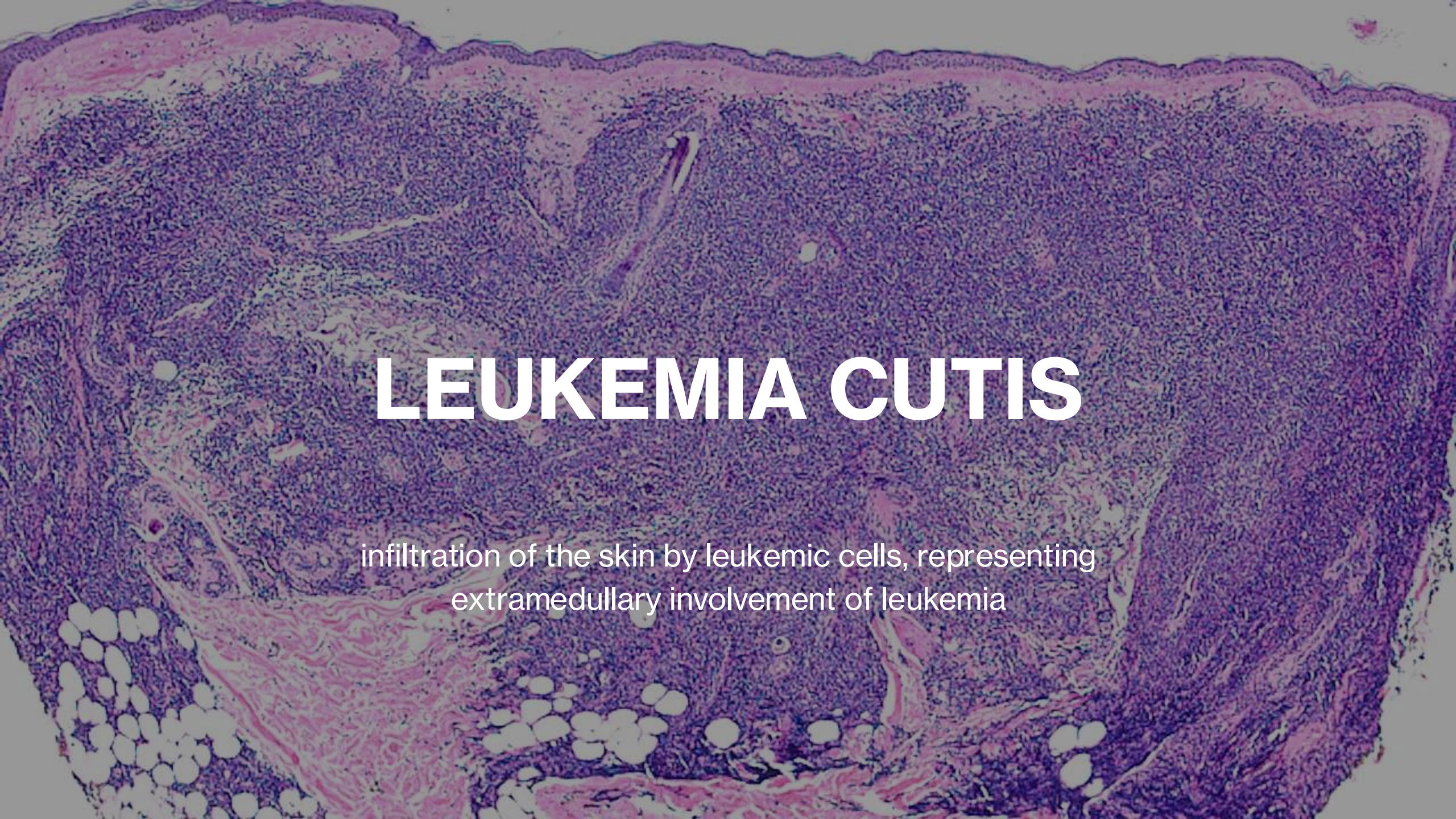
**EMPD** requires ruling out internal malignancy (especially if CK20+).

**IHC is crucial** (CK7, CK20, HER2, AR, GCDFP-15) for accurate diagnosis.

**Surgical excision** is mainstay, with adjuvant therapies based on tumor biology.

## Prognosis

- **MPD:**
  - Excellent prognosis if confined to nipple (5-year survival >90%).
  - Worse if invasive carcinoma present (depends on stage).
- **EMPD:**
  - **Primary EMPD:** Good prognosis if completely excised.
  - **Secondary EMPD:** Poorer prognosis (depends on underlying malignancy).
  - **Invasive EMPD:** Higher recurrence/metastasis risk.



# LEUKEMIA CUTIS

infiltration of the skin by leukemic cells, representing extramedullary involvement of leukemia

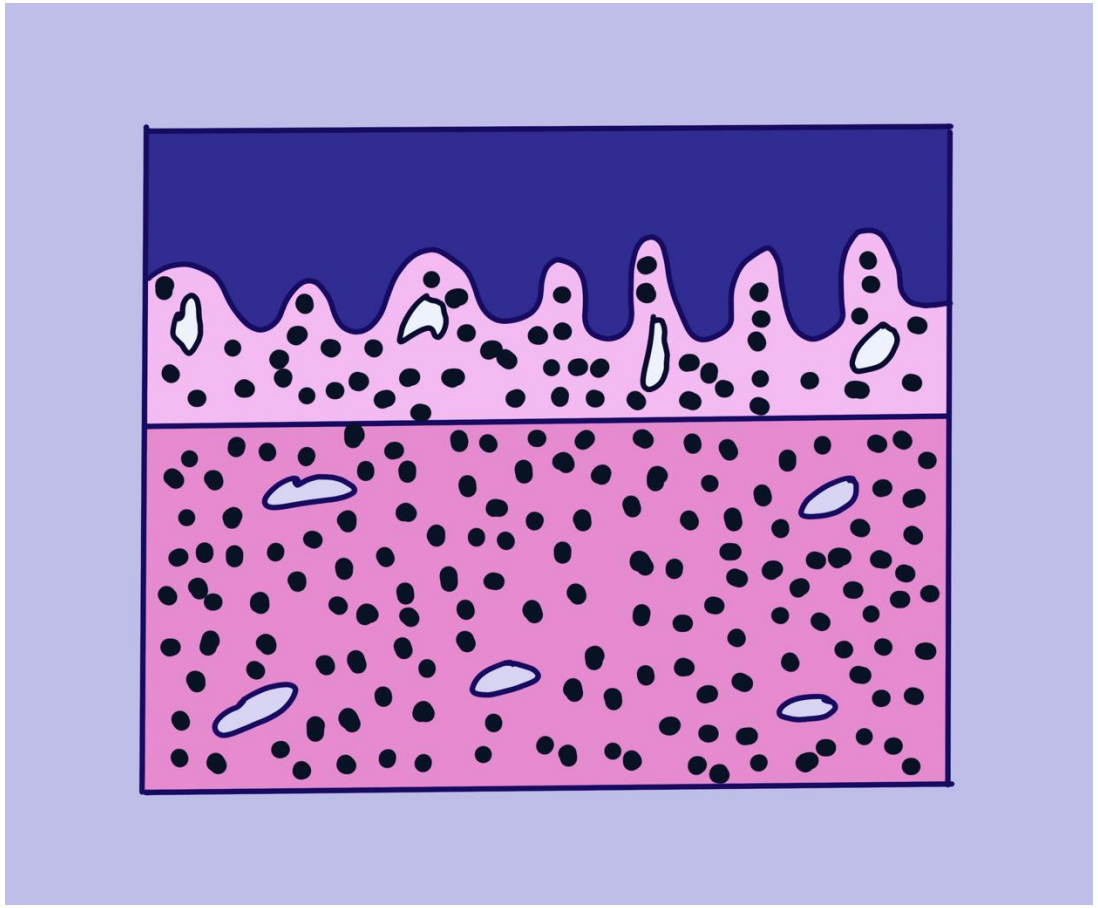
# Leukemia Cutis (LC)

- **Skin lesions**:
  - Erythematous, violaceous, or brown **papules, nodules, plaques, or ulcers**.
  - May resemble **leukocytoclastic vasculitis**, Sweet syndrome, or infections.
  - Common sites: **Trunk, extremities, face, scalp**.
- **Associated symptoms**:
  - Pruritus, pain, or asymptomatic.
  - Often indicates **aggressive disease** (poor prognosis in AML).

- **Common leukemia subtypes with LC**:
  - **AML (most common)**, especially **monocytic (M4/M5) subtypes**.
  - **CLL (B-cell chronic lymphocytic leukemia)**.
  - **T-cell leukemias (e.g., T-PLL, adult T-cell leukemia/lymphoma)**.
  - **Blastic plasmacytoid dendritic cell neoplasm (BPDCN)**.

# Leukemia Cutis (LC): Histopathology

- **Dense dermal infiltrates** (often sparing the epidermis = **"Grenz zone"**).
- **Pattern**:
  - **Perivascular & periadnexal** (early) → **Diffuse sheets** (late).
- **Cell morphology**:
  - **Myeloid leukemia (AML)**:
    - Immature myeloid cells with **fine chromatin, prominent nucleoli**.
    - **Auer rods** (if present, confirm myeloid lineage).
  - **Monocytic leukemia (AML-M4/M5)**:
    - Large, folded nuclei, abundant cytoplasm.
  - **CLL/SLL**:
    - Small, mature lymphocytes with **clumped chromatin**.
  - **T-cell leukemia**:
    - Atypical lymphocytes with **cerebriform nuclei** (e.g., Sézary-like in T-PLL).
  - **BPDCN**:
    - Medium-sized blasts with **plasmacytoid appearance**.



Lymphoma cutis
Leukemia cutis
Mast cell disease

# Leukemia Cutis (LC): Immunohistochemical (IHC) Markers

| Leukemia Type | Key IHC Markers |
|---|---|
| **AML** | MPO (+), CD68 (KP1/Lysozyme), CD117, CD34, CD43 |
| **Monocytic AML (M4/M5)** | CD14, CD163, CD68 (PGM1), Lysozyme |
| **CLL (Chronic Lymphocytic Leukemia) and SLL (Small Lymphocytic Lymphoma)** | CD20 (+), CD5 (+), CD23 (+), CD43 (+), **LEF1** (+) |
| **T-cell leukemia** | CD3 (+), CD4 (+), CD7 (often lost), CD52 (+) |
| **T-PLL** | CD3 (+), CD4 (+), CD52 (+), TCL1 (+) |
| **BPDCN** | **CD123** (strong +), **CD4** (+), **CD56** (+), TCL1 (+), TCF4 (+) |
| **Blastoid neoplasms** | TdT (+), CD34 (+), CD99 (+) (if lymphoblastic) |

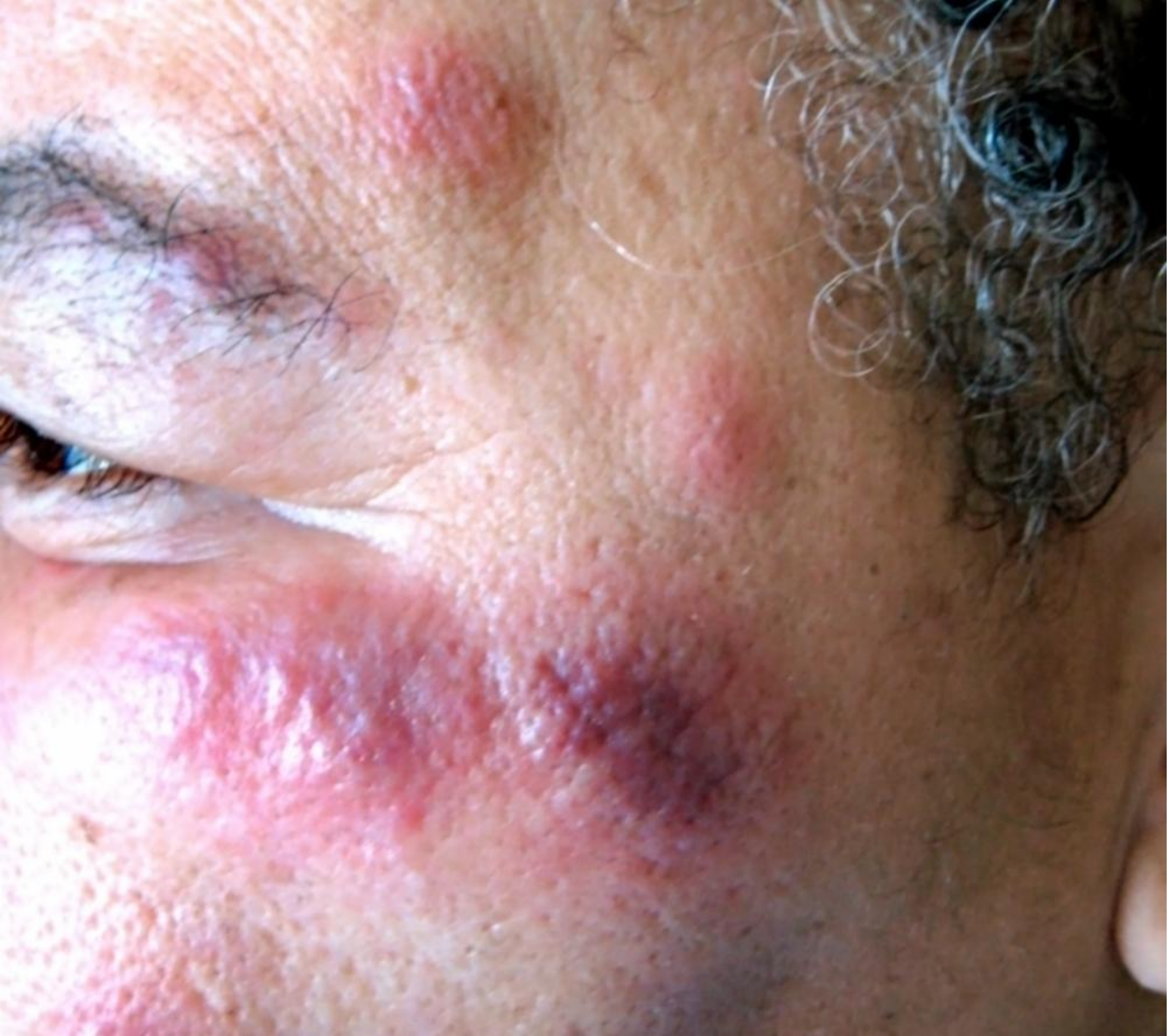
# Leukemia Cutis (LC)

## DIFFERENTIAL DIAGNOSIS

- **Cutaneous lymphoma** (e.g., mycosis fungoides vs. T-cell leukemia).
- **Granulocytic sarcoma** (extramedullary myeloid tumor, MPO+).
- **Reactive infiltrates** (e.g., Sweet syndrome, infection).

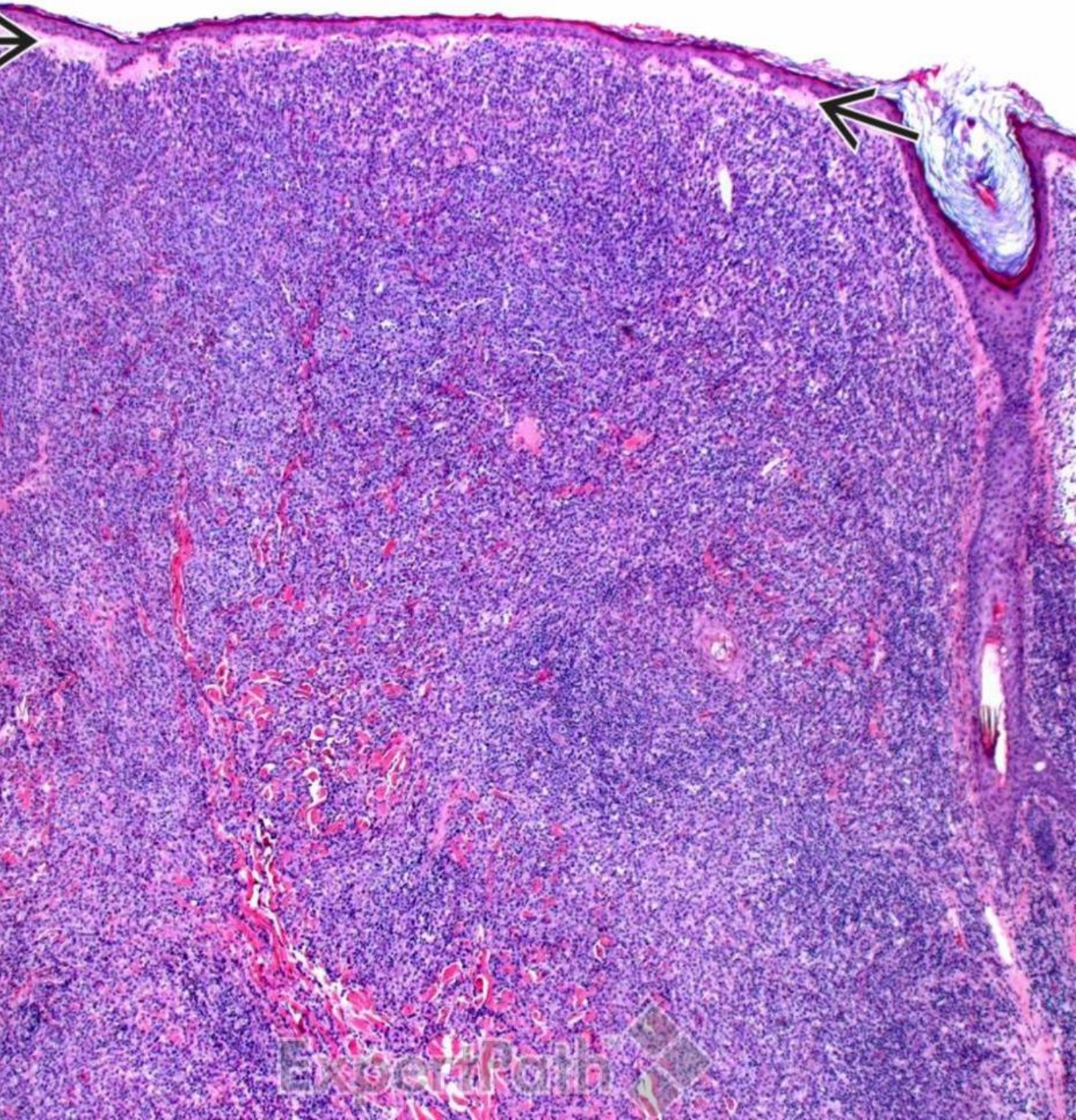
## PROGNOSIS

- LC often indicates **advanced/systemic disease** and poorer outcomes.
- **BPDCN** and **monocytic AML** have a high rate of skin involvement.



# Acute myelogenous leukemia

- Clinical photograph shows an adult male patient with a known history of AML who presented with multiple violaceous plaques on the face. (Courtesy M. Jackson, MD.)

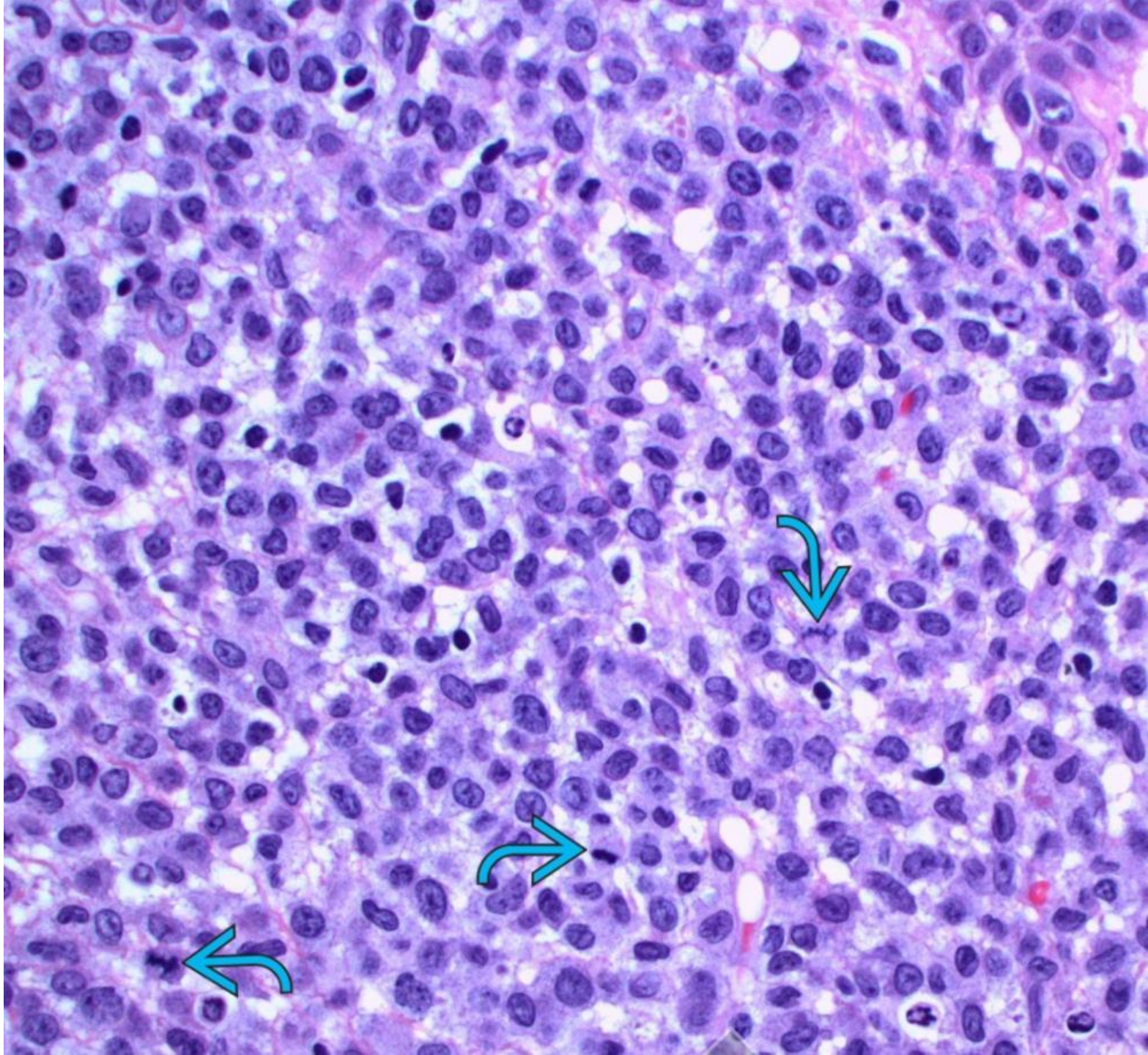



# Acute myelogenous leukemia

- Punch biopsy shows dense, atypical leukemic infiltrates in the superficial and deep dermis. Sparing of the epidermis with a thin grenz zone (black solid arrow) is noted. The cells at this power are small, atypical blue cells, which should raise consideration for a **lymphoma vs. leukemia vs. other small blue cell tumors, such as Merkel cell carcinoma**.

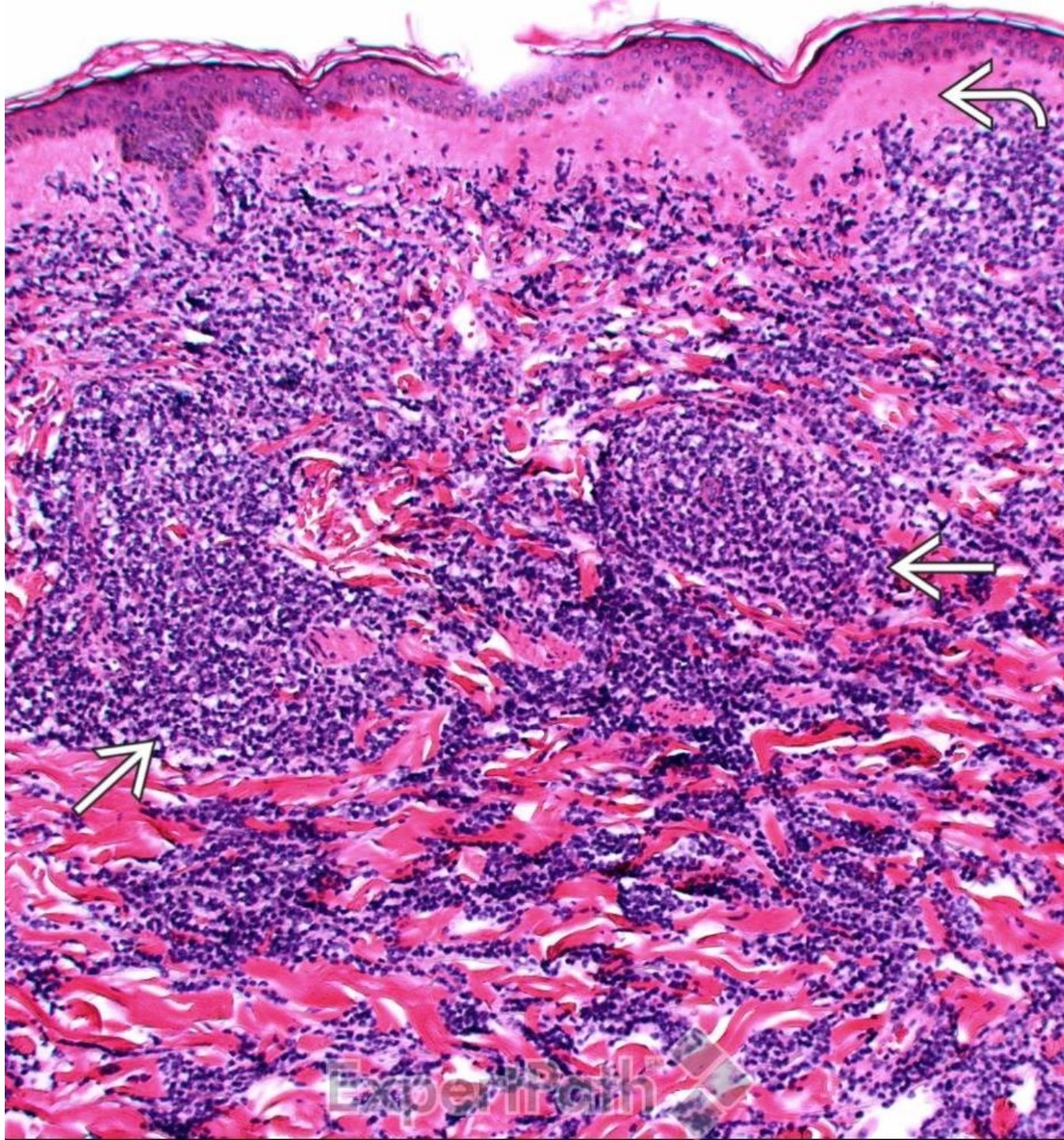
# Monocytic leukemia cutis

- High magnification shows atypical cells with round to oval nuclei and moderate amounts of pale to vacuolated cytoplasm, consistent with a monocytic leukemia cutis. Several mitotic figures (cyan curved arrow) are seen.



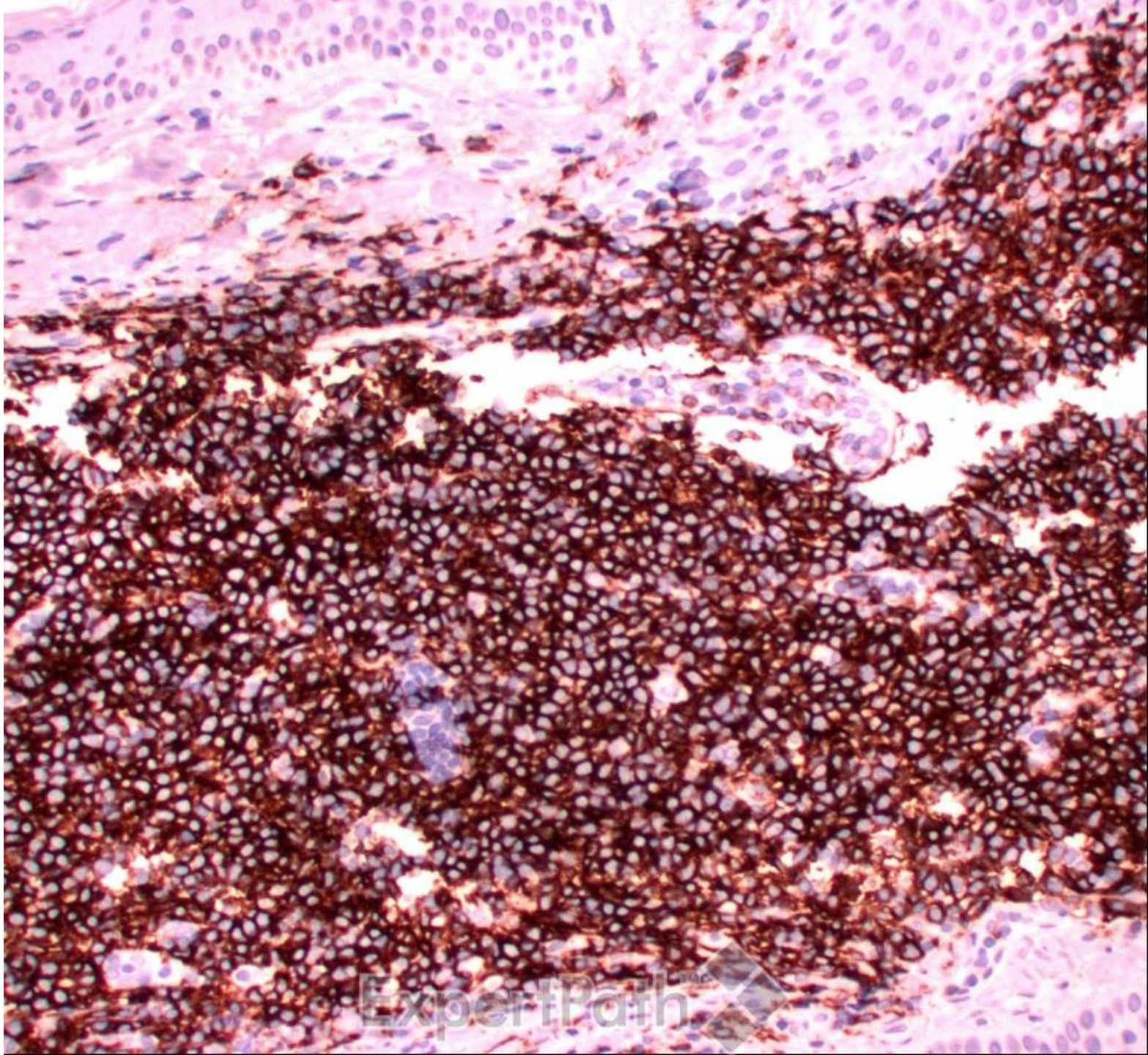
# Skin with involvement by CLL/SLL

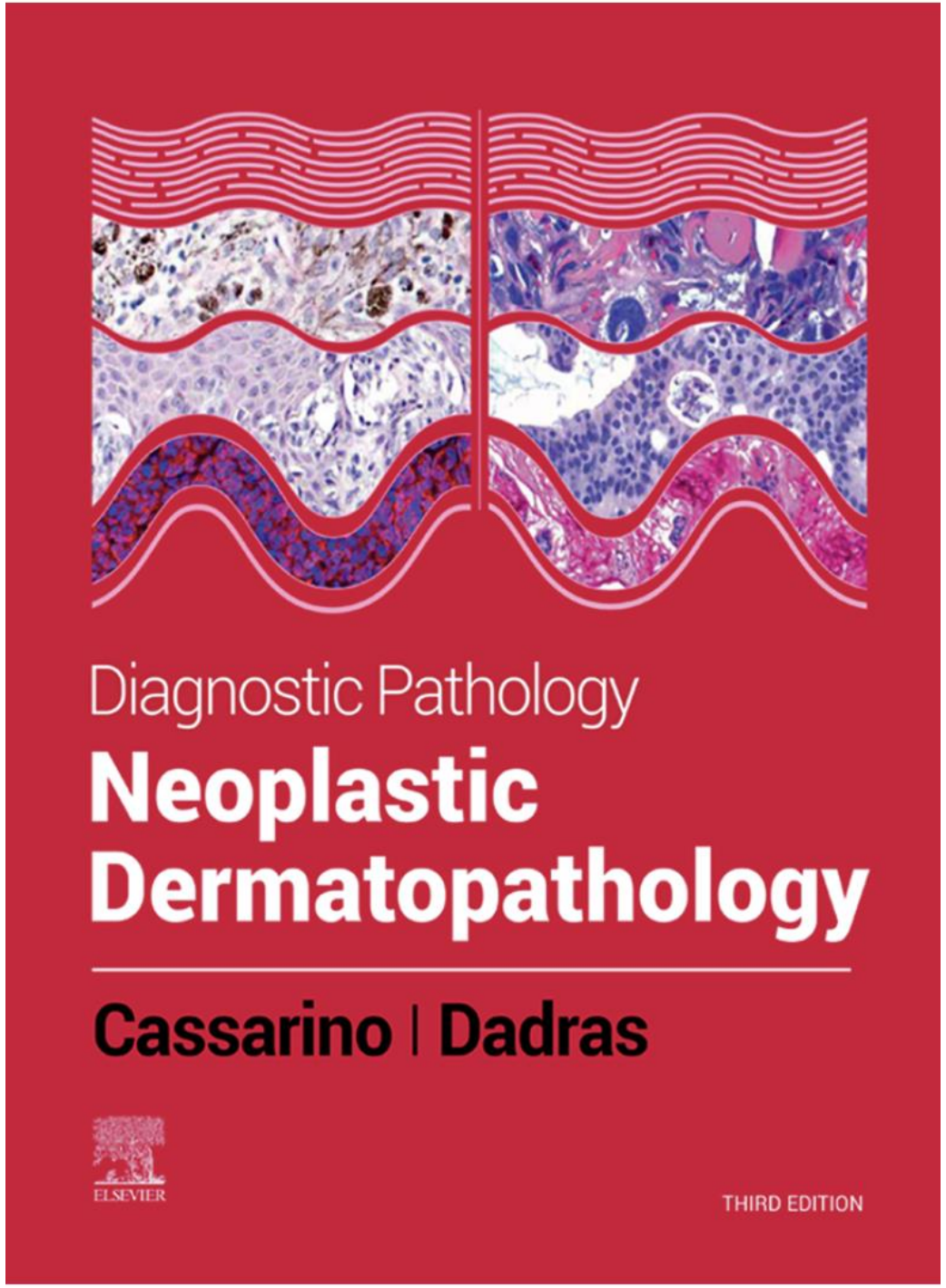
- The lymphoid cells (white solid arrow) are in the superficial and deep dermis and show a dense, sheet-like growth pattern. The epidermis is uninvolved and separated from the malignant B-cell infiltrate by a thin grenz zone (white curved arrow). No germinal centers are present.



# Skin with involvement by CLL/SLL

- The lymphoid infiltrate shows strong CD20 reactivity in a patient with CLL/SLL. The strong and diffuse reactivity is consistent with a mature B-cell lymphoma, although CD20 can also be aberrantly expressed in some B-LBLs.






# References

- 4th edition is in the works
- Image collections (S Dadras)
- https://digitalskinpathology.com/
  - Lecture posted
  - Topic relevant cases 102-109 posted