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Extramammary Paget's disease (EMPD)

By Valeria González-Molina, MD, Thomas Davis, MD, FAAD, and Rick Lin, DO, MPH, FAOCD

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- Rare adenocarcinoma typically found in apocrine gland-rich skin of the axilla and anogenital regions.

Primary	Secondary
Etiology: malignant pluripotent cells in the epidermis or adjacent adnexal structures. • In situ: confined to the epidermis • Micro-invasive: depth < 1 mm • Invasive: depth > 1 mm Primary EMPD can also be subclassified as: (1) intraepithelial EMPD (in situ or micro-invasive), (2) invasive primary EMPD, or (3) EMPD with underlying adnexal adenocarcinoma.	Etiology: extension of an adjacent visceral malignancy.

Epidemiology:

- Age: 50-80 years old
- Populations: elderly Caucasian women; distinct male predominance in Asian cohorts.

Clinical features:

- Slow growing, ill-defined, erythematous nodules or plaques with islands of hypo- or hyperpigmentation and occasional scale-crust, erosion, or ulceration.
- Described changes classically produce a "strawberries and cream" appearance.
- Most common sites of EMPD: vulva, penoscrotal, perianal, umbilical, inguinal, axillary, and truncal regions.
- Can be asymptomatic or associated with pruritus, dysesthesia, or pain.
- Can mimic common inflammatory and infectious dermatoses as well as other more commonly encountered NMSCs.

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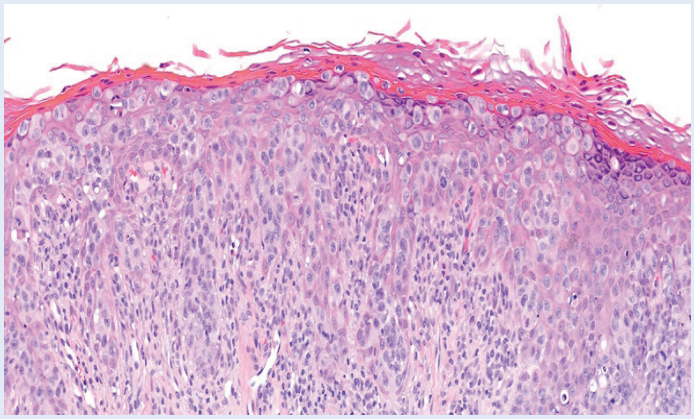
Clinical Ddx: Lichen simplex chronicus, inverse psoriasis, erosive lichen planus, pemphigus vegetans, candidiasis, irritant contact dermatitis, dermatophytosis, superficial basal cell carcinoma, squamous cell carcinoma *in-situ*.

Histological features:

- Atypical cells with hyperchromatic nucleus and abundant pale-staining cytoplasm ("pagetoid cells") in pagetoid growth pattern within the epidermis (*in situ* EMPD) and dermis/subcutis (invasive EMPD).
- Atypical cells may "spit out" into the stratum corneum intact.
- May exhibit noncontiguous spread, necessitating scouting biopsies to help define the extent of involvement



- Pagetoid cells stain positive for PAS (diastase-resistant), Alcian blue, and toluidine blue (at high pH)
- Diagnostic IHC panel: See algorithm below on approaching pagetoid differentials with IHC.

Prognosis: Despite a high recurrence rate, the prognosis is favorable in the absence of an underlying visceral or adnexal carcinoma.

Poor prognosis:

- Depth of invasion >1 mm
- Lympho-vascular invasion
- Lymph node metastasis

5-year disease-specific survival:

92%: Local disease

77%: Regional metastases

7-16%: Distant metastasis

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Work-up

- A thorough physical examination of the affected area and surrounding anatomical sites is essential. This includes palpating the regional lymph nodes.
- Sentinel lymph node biopsy (SLNB) is not recommended for *in situ* and microinvasive EMPD but is indicated for invasive EMPD. If clinical lymphadenopathy is detected, appropriate imaging and tissue sampling should be done.
- Age-appropriate cancer screenings are advised.

Recommended work-up to rule out secondary EMPD based on location of the primary lesion:

	Perianal	Vulvar	Penoscrotal
Baseline	-Colonoscopy or rectosigmoidoscopy -CT chest/abdomen/pelvis	-Mammogram -Urinalysis/cytology -Pap smear	-PSA <70 years -Urinalysis/cytology -Heme-occult test
High risk*	-Urinalysis/cytology	-Heme-occult test -Cystoscopy -Proctoscopy	-Colonoscopy -Cystoscopy -CT chest/abdomen/pelvis

**CK20+, dermal invasion > 1 mm, lymphadenopathy, clinical nodules, bilateral groin involvement, mucosal extension*

Management:

Surgical approaches

- Mohs micrographic surgery (MMS)
- Surgery with complete circumferential peripheral and deep margin assessment (CCPDMA)
- Wide local excision (WLE)

Recurrence rate:

- 11% MMS
- 18% CCPDMA
- 37% WLE

Margins recommended for 95% clearance:

- Penoscrotal and vulvar: 4 cm
- Perianal and axillary: 3.5 cm

Non-surgical approaches

- Photodynamic therapy (PDT): 5-aminolevulinic acid
- Radiation (monotherapy or adjuvant therapy for surgical excision with positive margins or tumors with high-risk histologic features)
- Laser ablation: carbon dioxide, Nd:YAG

Topical agents:

- Imiquimod cream (5%)
- 5-Fluorouracil cream (5%)l
- Calcipotriene, tretinoin, and rapamycin in combination with 5% imiquimod or 5% 5-fluorouracil
- Bleomycin cream/ointment (3.5%)

Recommended follow-up: Skin exam and regional lymph node exam.

- Every 3-6 months for the first 3 years, followed by
- Every 6-12 months until 5 years from diagnosis

Periodic ultrasound for high-risk patients with invasive EMPD.

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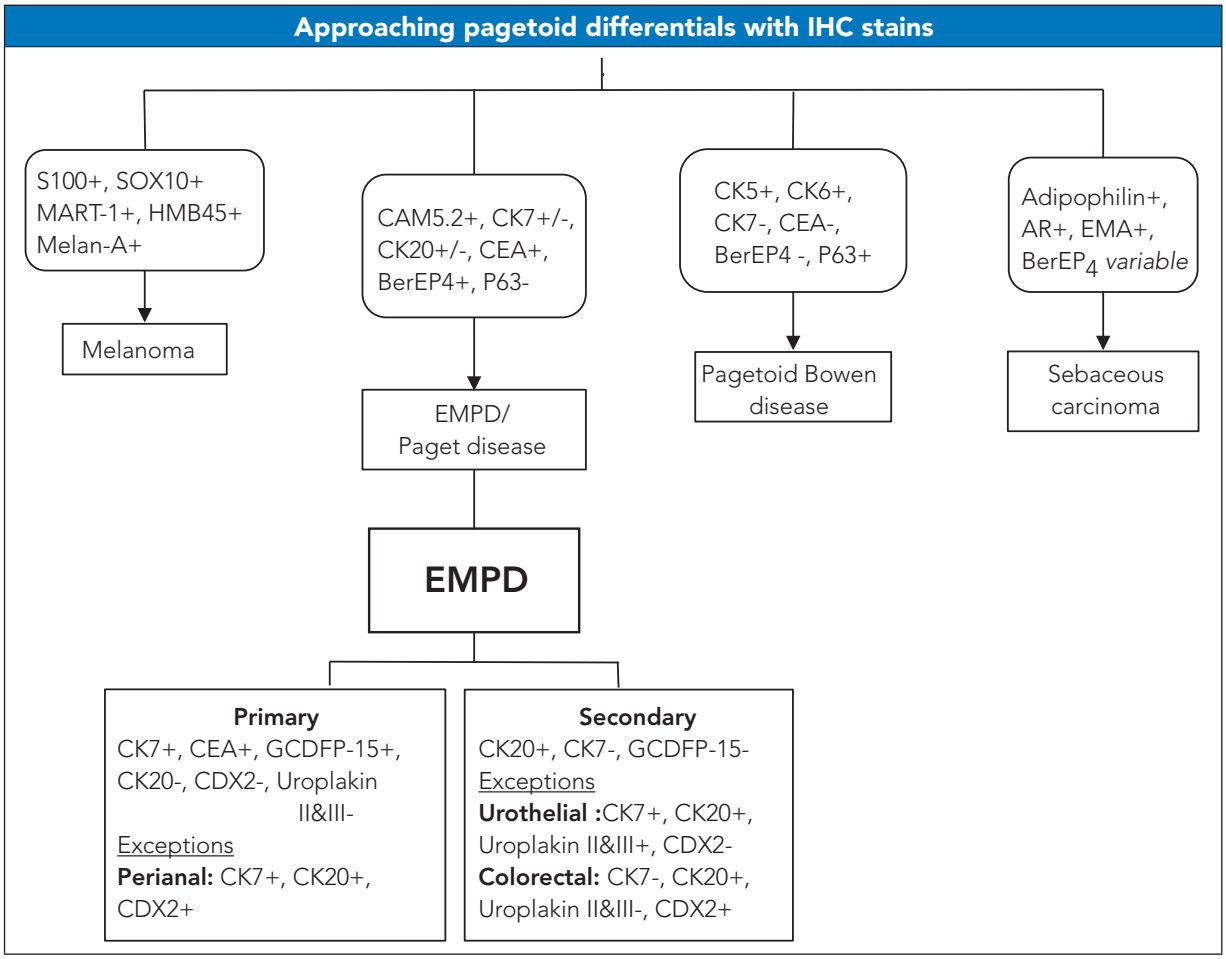

Additional points:

- All patients with EMPD should be evaluated for underlying internal malignancy, regardless of IHC staining profiles.
- Ectopic EMPD may occur in areas without apocrine glands (extremities, etc.).
- Patients with metastatic disease should be referred for multidisciplinary tumor board consultation with consideration of enrollment in clinical trials.
- HER2 amplification has been associated with more invasive disease, higher risk for lymph node metastases, and reduced overall survival.
- A case series of four patients with invasive vulvar EMPD treated with trastuzumab (a monoclonal antibody targeting HER2) and weekly paclitaxel was safe and effective for treating HER2-positive EMPD.

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