Brown macule on vulva of an elderly woman

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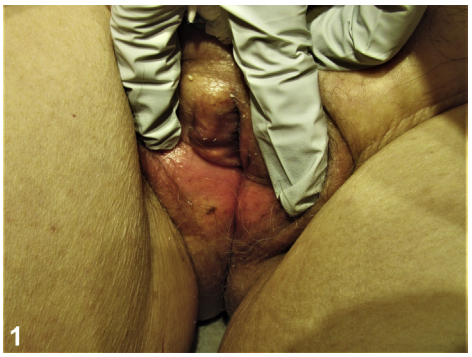
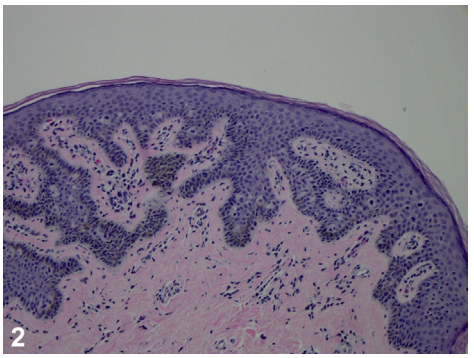
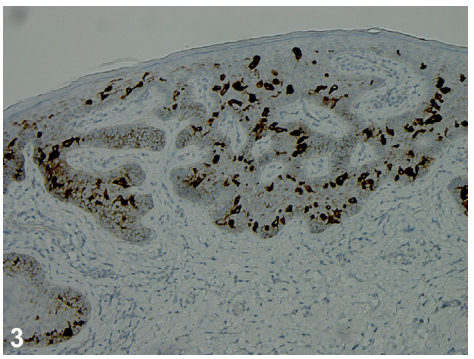
A 90-year-old white woman presented to our outpatient dermatology clinic for her annual complete cutaneous examination. The patient had no concerns at her visit. However, physical examination found a 4.0- × 2.5-mm brown macule on her right inner labia majora that was not present on her previous examination 1-year prior (Fig 1). The patient denied knowing if the lesion had grown or changed in size, shape, or color and stated that she was unaware the lesion was present. Additionally, the patient denied any associated burning, itching, pain, or bleeding in the involved area.







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Question 1: Based on the above information, which of the following is the most likely diagnosis?

A. Pigmented extramammary Paget disease (EMPD)

B. Melanoma

C. Seborrheic keratosis

D. Vulvar intraepithelial neoplasia (VIN)

E. Pigmented basal cell carcinoma

Answers:

A. Pigmented EMPD — Correct. EMPD is an intraepithelial adenocarcinoma that typically affects postmenopausal women.[1] EMPD most commonly occurs on the vulva, but additional sites of involvement include other apocrine gland-containing regions such as the axilla, perianal region, and penis.[2] Classically, EMPD manifests as a well-demarcated, erythematous plaque with an average diameter of 5 cm.[3] However, atypical presentations of nodules, atrophic plaques, and pigmented lesions have been reported. There are currently 11 well-documented cases of pigmented EMPD in the literature.[4] In contrast to classic EMPD, the cases of EMPD presenting as pigmented lesions exhibited nearly equal sex distribution. Two cases of pigmented EMPD arose in non-apocrine–bearing sites, heightening the diagnostic challenge these cases represent.[4]

B. Melanoma — Incorrect. Melanoma would demonstrate a broad lesion with atypical melanocytes scattered within the epidermis with ample amphophilic cytoplasm. Melan-A/MART1 immunohistochemical stains identify melanocytes.[5]

C. Seborrheic keratosis — Incorrect. There are 6 seborrheic keratosis variants (acanthotic, hyperkeratotic, reticulated, irritated, clonal, and melanoacanthoma). All show varying degrees of hyperkeratosis, papillomatosis, and acanthosis. Horn pseudocysts are characteristically present.[6]

D. VIN — Incorrect. Infection with high-risk human papillomavirus may lead to vulvar intraepithelial neoplasia that exists on a spectrum from VIN grade 1 to VIN grade III, which demonstrates pleomorphism, nuclear enlargement, and hyperchromasia confined to the basal epidermis or completely replacing the epithelium, respectively.[7]

E. Pigmented basal cell carcinoma — Incorrect. Pigmented BCC shows collections of basaloid keratinocytes within a fibromyxoid stroma between tumor islands. Retraction artifact is often seen when the tumor stroma separates from the tumor islands, seen as clear spaces or clefts. In the pigmented variant, melanin, melanocytes, and/or melanophages are irregularly dispersed throughout the epidermis and dermis.[8]

Question 2: All of the following are included in the histopathologic differential diagnosis of pagetoid spread, demonstrated in Figs 2 and 3, except:

A. Melanoma

B. Squamous cell carcinoma in situ

C. Sebaceous carcinoma

D. EMPD

E. Mycosis fungoides

Answers:

A. Melanoma — Incorrect.

B. Squamous cell carcinoma in situ — Incorrect.

C. EMPD — Incorrect.

D. Sebaceous carcinoma, Incorrect.

Histopathologically, EMPD demonstrates hyperkeratosis and epidermal hyperplasia with a dual cell population of Paget cells and keratinocytes. The keratinocytes are flat, mitotically active, and compressed, whereas the Paget cells appear glandular with amphophilic to basophilic cytoplasm and situate mostly along the basal and parabasal zones.[1] A characteristic feature of EMPD is intraepidermal proliferation of epithelioid cells with abundant cytoplasm and enlarged nuclei with prominent nucleoli.[4] Paget cells are highlighted by epithelial membrane antigen (EMA) immunohistochemical stain.[1] Other cutaneous neoplasms with pagetoid spread to consider in the differential diagnosis are melanoma, squamous cell carcinoma in situ, sebaceous carcinoma, and Langerhans cell histiocytosis.[9]

E. Mycosis fungoides — Correct. Mycosis fungoides histopathologically shows a band-like lymphocytic superficial infiltrate. Atypical lymphocytes

are present in the epidermal basal layer and sporadically spread throughout the epidermis, demonstrating epidermotropism and not pagetoid spread.[10]

Question 3: To help further characterize the etiology of this diagnosis (primary vs secondary) additional immunohistochemical stains are required. Which of the following staining pattern is most consistent with a primary cutaneous process?

A. +CK7, +CK20, -GCDFP-15, −CEA, −uroplakin III

B. +CK7, −CK20, +GCDFP-15, +CEA, −uroplakin III

C. −CK7, +CK20, +GCDFP-15, +CEA, +uroplakin III

D. −CK7, −CK20, +GCDFP-15, +CEA, −uroplakin III

E. +CK7, +CK20, +GCDFP-15, +CEA, −uroplakin III

Answers:

A. +CK7, +CK20, −GCDFP-15, −CEA, −uroplakin III − Incorrect. GCDFP-15 and CEA are positive, whereas CK20 is negative in primary cutaneous EMPD.

B. +CK7, −CK20, +GCDFP-15, +CEA, −uroplakin III − Correct.

C. −CK7, +CK20, +GCDFP-15, +CEA, +uroplakin III − Incorrect. CK7 is positive, whereas CK20 and Uroplakin III are negative in primary cutaneous EMPD.

D. −CK7, −CK20, +GCDFP-15, +CEA, −uroplakin III − Incorrect. CK7 is positive in primary cutaneous EMPD.

E. +CK7, +CK20, +GCDFP-15, +CEA, −uroplakin III − Incorrect. CK20 is negative in primary cutaneous EMPD.

Once the diagnosis of EMPD has been established histopathologically, immunohistochemical stains are used to determine whether it is a primary process or secondary to an underlying malignancy (Table I).[1]

Table I. Immunohistochemical staining pattern of primary versus secondary EMPD

	Positive	Negative
Primary EMPD	CK7 GCDFP-15 CEA	CK20 Uroplakin III
Secondary EMPD anorectal origin	CK20 CEA	CK7 GCDFP-15 Uroplakin III
Secondary EMPD urothelial origin	CK7 Uroplakin III ±CK20	GCDFP-15 CEA

Abbreviations used:

EMPD: extramammary Paget disease
VIN: Vulvar intraepithelial neoplasia

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