Pathologic Quiz Case

A 63-Year-Old Woman With a Pigmented Perineal Lesion

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A 63-year-old woman presented to her gynecologist for a painful, nonhealing perineal lesion. The patient's past medical history was most notable for hypertension, diabetes, oxygen-dependent emphysema, and total abdominal hysterectomy and bilateral salpingo-oophorectomy 13 years previously for leiomyomata. Physical examination revealed a red-brown roughened area of 3 to 4 cm in diameter on the left posterior vulvar/perineal area approximately 0.5 cm from the anus. A 0.5-cm punch biopsy was performed.

A hematoxylin-eosin–stained section of the skin biopsy showed large cells with irregular, markedly atypical nuclei and pale cytoplasm, either singly or in clusters within the epidermis (Figure 1). These cells had large nuclei with prominent nucleoli and coarsely clumped chromatin. The cytoplasm was vacuolated, and melanin pigment was noted in some tumor cells (Figure 2). Dermal invasion was not observed in the biopsy.

What is your diagnosis?

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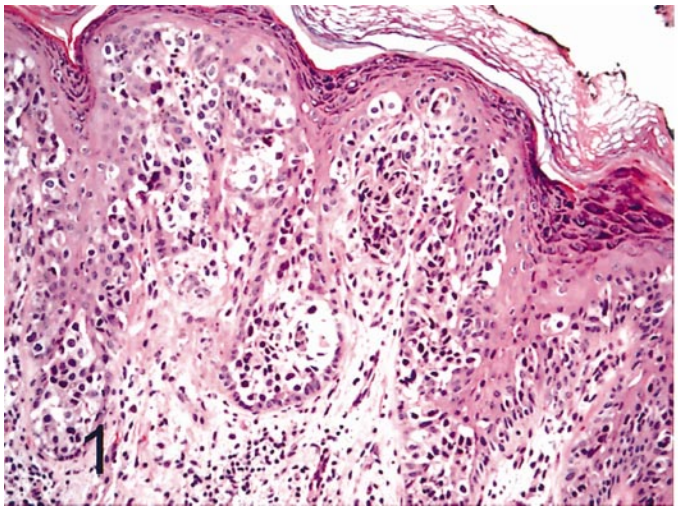

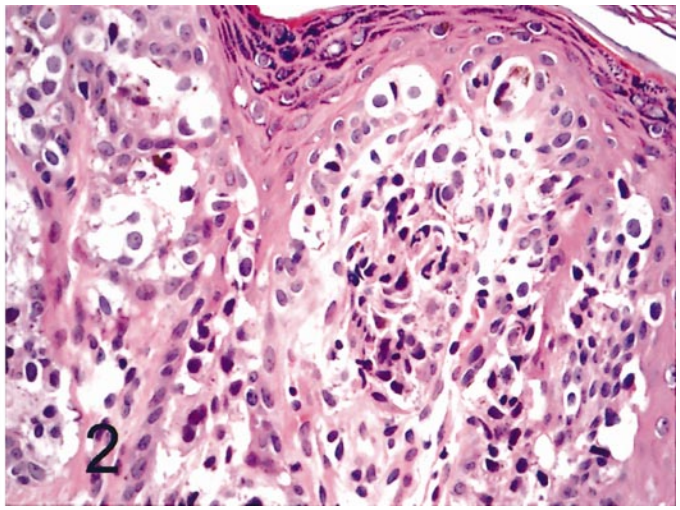

Pathologic Diagnosis: Extramammary Paget Disease

The biopsy was initially interpreted at a commercial laboratory as ''predominantly junctional melanocytic proliferation with severe cytologic atypia and features most consistent with malignant melanoma in situ, superficial spreading type.'' No immunostains were performed at that time. On consultative review, immunohistochemical evaluation revealed that the tumor cells were positive for carcinoembryonic antigen. Prominent pigmented melanocytes with elongated processes enveloping the tumor cells were more readily identified in the immunostained slides that were negative for MART-1 and HMB-45.

Paget disease was originally described as a breast lesion with associated underlying invasive ductal adenocarcinoma, but it was later classified according to the location on the body as mammary or extramammary disease.[1] Extramammary Paget disease often involves the anogenital skin, especially the vulva and perineal area.[2] Paget disease of the vulva is a rare condition, comprising only 1% to 2% of vulvar malignancies, and it is most commonly encountered in postmenopausal white women, with a median age of 70 years.[3,4] Clinically, vulvar Paget disease can present as an erythematous lesion, as an eczematous lesion with red to pink areas sometimes accompanied by white islands of hyperkeratosis, or both.[4] The lesions may occur as unifocal or multifocal areas anywhere on the vulva.[5]

Vulvar Paget disease and pagetoid urothelial intraepithelial neoplasia have recently been subclassified into 3 distinct types based on the origin of the neoplastic cells, namely (1) primary vulvar cutaneous Paget disease; (2) Paget disease as a manifestation of an associated adjacent primary anal, rectal, or other noncutaneous adenocarcinoma; or (3) pagetoid urothelial intraepithelial neoplasia, also referred to as pseudo-Paget disease or Paget disease as a manifestation of bladder (urothelial) neoplasia.[4,6]

Primary vulvar Paget disease is characterized by an intraepithelial proliferation of atypical glandular cells and is considered by the World Health Organization as a glandular variant of vulvar intraepithelial neoplasia (adenocarcinoma in situ). Histologically, it is characterized by relatively large cells, often with abundant cytoplasm, which are located within the otherwise normal squamous epithelium. These cells are generally larger than the adjacent keratinocytes and have large, atypical nuclei with prominent nucleoli. Their cytoplasm is finely granular, amphophilic to basophilic, and often vacuolated. The neoplastic cells are typically clustered in groups or dispersed as single cells within the epithelium, occasionally actually forming glandlike structures.[4]

Paget cells are positive for periodic acid–Schiff (diastase resistant), mucicarmine, aldehyde fuchsin, and Alcian blue. The Paget cells stain positively for carcinoembryonic antigen, cytokeratin 7, and gross cystic disease fluid protein-15, and they typically are negative for S100 protein, HMB-45, MART-1, and Melan-A. These histochemical and immunohistochemical reactions help to distinguish Paget disease from vulvar intraepithelial neoplasia, superficial spreading malignant melanoma, and pagetoid reticulosis (a variant of cutaneous T-cell lymphoma). Melanomas usually are immunoreactive for S100 protein, HMB-45, Melan-A, and MART-1, whereas Paget disease, vulvar intraepithelial neoplasia, and pagetoid reticulosis are negative. Paget cells may contain intracytoplasmic melanin granules, probably produced by neighboring melanocytes and engulfed secondarily by the Paget cells.[4] Alternatively, melanin containing melanocytic dendritic processes surrounding the Paget cells may render the lesion pigmented, leading to misdiagnosis as a primary melanocytic lesion, as illustrated by our case.

For this reason, any vulvar or perineal lesion in which the distinction between a melanocytic neoplasm and true Paget disease is unclear should be subjected to immunohistochemical staining with a combination of S100 protein, HMB-45, Melan-A, MART-1, carcinoembryonic antigen, and gross cystic disease fluid protein-45.

References

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