

## What Is Your Diagnosis?



An 81-year-old woman presented for evaluation of a nodule on the right labia majora that had been present for 1 year. She had a history of intertriginous psoriasis, and several biopsies were performed at an outside facility over the last 5 years that revealed psoriasis but were otherwise noncontributory. Physical examination revealed erythema and scaling on the buttocks with maceration in the intertriginous area (top) and the perineum associated with a verrucous nodule (bottom).

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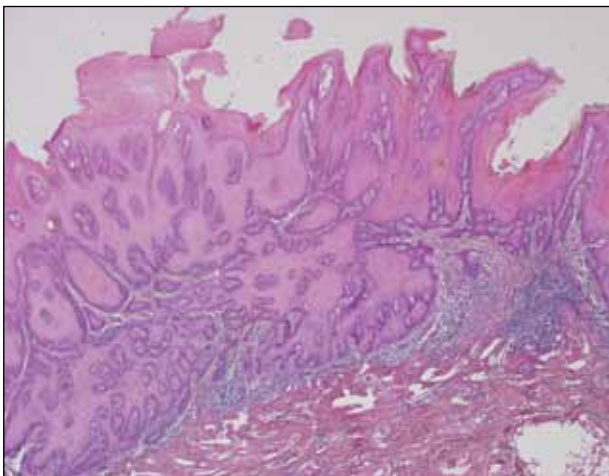
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## The Diagnosis: Verrucous Carcinoma

**B**iopsies of early lesions often may be difficult to interpret without clinicopathological correlation. Our patient's tumor was associated with intertriginous psoriasis, which was the only abnormality previously noted on superficial biopsies performed at an outside facility. The patient was scheduled for an excisional biopsy due to the large tumor size and clinical suspicion that the prior biopsies were inadequate and failed to demonstrate the primary underlying pathology. Excisional biopsy of the verrucous tumor revealed epithelium composed of keratinocytes with glassy cytoplasm. Papillomatosis was noted along with an endophytic component of well-differentiated epithelial cells extending into the dermis in a bulbous pattern consistent with the verrucous carcinoma variant of squamous cell carcinoma (SCC)(Figure). Verrucous carcinoma often requires correlation with both the clinical and histopathologic findings for definitive diagnosis, as keratinocytes often appear to be well differentiated.<sup>1</sup> In cases that have gone undiagnosed with a large tumor, increased nuclear atypia may become evident with areas of nuclear pleomorphism and individual cell dyskeratosis.

Verrucous carcinoma may begin as an innocuous papule that slowly grows into a large fungating tumor. Verrucous carcinomas typically are slow growing,



Excisional biopsy of the verrucous nodule revealed marked acanthosis of the epidermis and bulbous projections of epithelium extending into the dermis. The endophytic "pushing border" supported a diagnosis of verrucous carcinoma (H&E, original magnification  $\times 100$ ).

and exophytic, and low grade. The etiology of verrucous carcinoma is not clear, and the role of human papillomavirus (HPV) infection is controversial.<sup>2</sup> Best classified as a well-differentiated SCC, verrucous carcinoma rarely metastasizes but may invade adjacent tissues.

Differential diagnoses include a giant inflamed seborrheic keratosis, condyloma acuminatum, rupioid psoriasis, and inflammatory linear verrucous epidermal nevus (ILVEN). Although large and inflamed seborrheic keratoses may have squamous eddies that mimic SCC, seborrheic keratoses do not invade the dermis and typically have a well-circumscribed stuck-on appearance. Abnormal mitotic figures are not identified. Condylomas are genital warts caused by HPV infection that often are clustered, well circumscribed, and exophytic. Large lesions can be difficult to distinguish from verrucous carcinomas, and biopsy generally reveals koilocytes identified by perinuclear clearing and raisinlike nuclei. Immunohistochemical staining and in situ hybridization studies can be of value in diagnosis and in identifying those lesions that are at high risk for malignant transformation. High-risk condylomas are associated with HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, and HPV-39, as well as other types, whereas low-risk condylomas are associated with HPV-6, HPV-11, HPV-42, and others.<sup>2</sup> Differentiating squamous cell hyperplasia from squamous cell carcinoma in situ also can be aided by immunohistochemistry. Squamous cell hyperplasia is usually negative for INK4 p16<sup>Ink4A</sup> and p53 and exhibits variable Ki-67 staining. Differentiated squamous cell carcinoma in situ exhibits a profile that is p16<sup>Ink4A</sup> negative, Ki-67 positive, and exhibits variable p53 staining.<sup>3</sup> Basaloid and warty intraepithelial neoplasia is consistently p16<sup>Ink4A</sup> positive, Ki-67 positive, and variably positive for p53.<sup>3</sup> Therefore, p16 staining of high-grade areas is a useful biomarker that can help establish diagnosis of associated squamous cell carcinoma.<sup>4</sup> The role of papillomaviruses in the development of nonmelanoma skin cancer is an area of active study, and research suggests that papillomaviruses may have a much greater role than previously suspected.<sup>5</sup>

At times, psoriasis may be markedly hyperkeratotic, clinically mimicking a verrucous neoplasm. This hyperkeratotic type of psoriasis is known as rupioid psoriasis. However, these psoriatic lesions are exophytic, are associated with spongiform pustules, and lack the atypia and endophytic pattern typically seen with verrucous carcinoma. An ILVEN also lacks atypia and an endophytic pattern and usually presents in childhood

as a persistent linear plaque, rather than the verrucous plaque noted in our patient. Squamous cell carcinoma has been reported to arise in the setting of verrucoid ILVEN but is exceptionally uncommon.<sup>6</sup>

Successful treatment of verrucous carcinoma is best achieved by complete excision. Oral retinoids and immunomodulators such as imiquimod also may be of value.<sup>7</sup> Our patient's tumor qualifies as T2N0M0 because it was greater than 2 cm in size.<sup>8</sup> A Breslow thickness of 2 mm or greater and Clark level IV are high-risk features associated with a worse prognosis, but clinical evaluation of our patient's lymph nodes was unremarkable and no distant metastases were identified. Our patient continues to do well with no evidence of recurrence.

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