Multinucleated Atypia of the Vulva

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Multinucleated atypia of the vulva (MAV) is an entity with a distinctive histologic pattern of multinucleation in the basal and middle layers of the squamous epithelium that may mimic human papillomavirus (HPV)–related squamous atypias. MAV is rarely reported in the literature, and we believe it should be considered in the differential diagnosis of flesh-colored vulvar papules and vulvar epidermal atypias with multinucleated squamous cells. We describe the case of a 49-year-old patient with the diagnosis of MAV. Results of histopathologic examination revealed a focal area of multinucleation in the basal to middle epithelial layers of the vulvar squamous epithelium, accompanied by mild hyperkeratosis and chronic inflammation. HPV was not identified in the lesion by in situ hybridization techniques.
Cutis. 2005;75:118-120.

Nuclear atypia of the vulvar squamous epithelium typically is present as a component of a human papillomavirus (HPV)–induced condyloma acuminatum or vulvar intraepithelial neoplasia (VIN) or as a reactive phenomenon in inflammatory skin disorders of various causes. According to the International Society for the Study of Vulvar Diseases and the Nomenclature Committee for the International Society of Gynecological Pathologists, the former disorders are classified as VIN (including both VIN and condyloma acuminatum); the latter includes non-neoplastic epithelial disorders (vulvar dystrophies), as well as other types of vulvar dermatoses.[1] We describe a postmenopausal patient with clinically discrete vulvar lesions and a peculiar type of squamous nuclear atypia that has been reported as multinucleated atypia of the vulva (MAV).

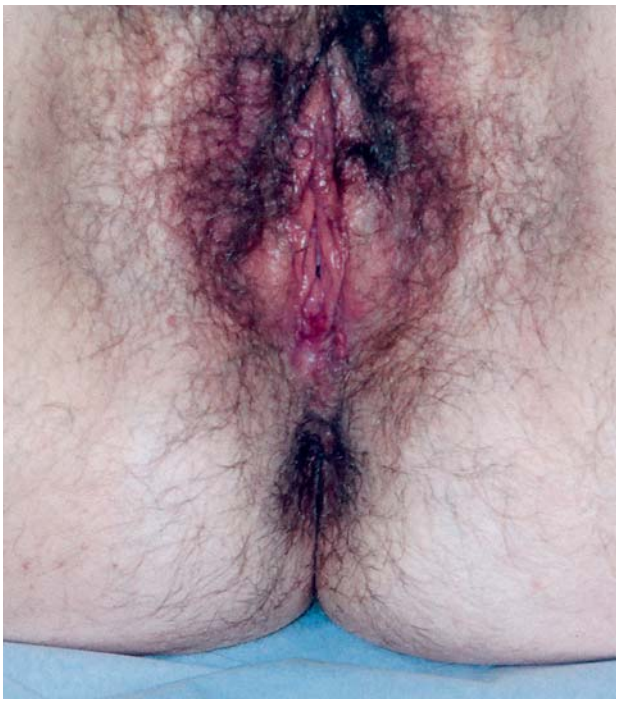

Figure 1. Bilateral flesh colored flat-topped papules on the labia of a 49-year-old woman.

Case Report

A 49-year-old postmenopausal woman presented with vulvar irritation and redness. She reported that small tender nodules had gradually developed on both sides of her labia over the previous 3 years. The patient's gynecologic history was significant for menometrorrhagia requiring daily pad usage that had persisted for 8 years; an abnormal finding on a Pap smear demonstrating a few scattered dysplastic squamous cells that had prompted treatment with cryotherapy in 1987; and frequent vaginal infections over the past year. Her dermatologic history was notable for acne vulgaris and herpes zoster infections but did not include herpes simplex infection. The remainder of her medical history was unremarkable.

Accepted for publication January 5, 2004.
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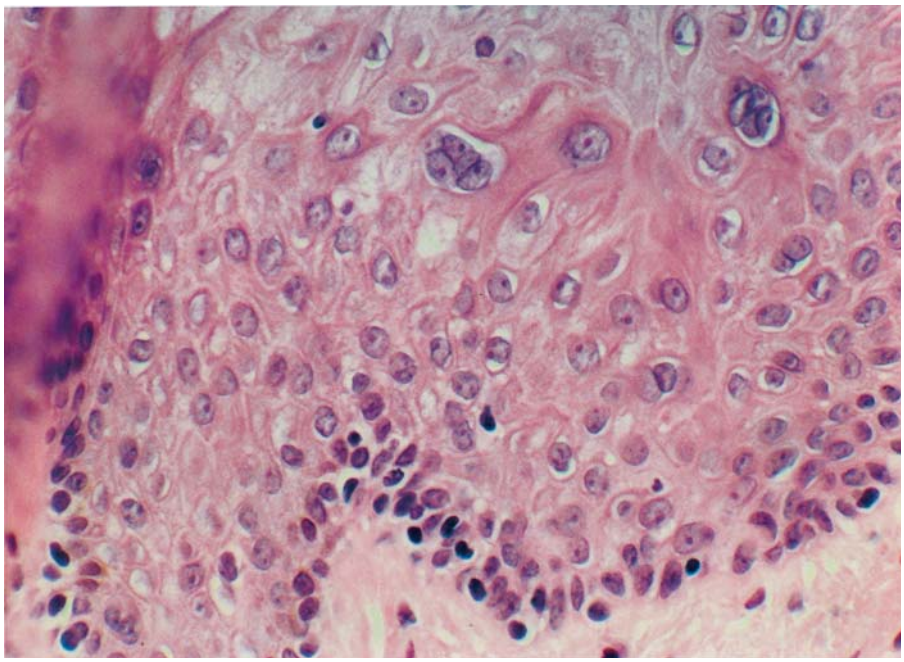

Figure 2. Biopsy of multinucleated atypia of the vulva demonstrates focus of multinucleated cells in the basal to middle layers of the epidermis (H&E, original magnification ×40).

Findings from a physical examination included several scattered 3- to 5-mm flesh colored flat-topped papules distributed bilaterally on the labia minora and majora (Figure 1).

Tissue for light microscopy was fixed with formalin, embedded in paraffin, and processed routinely, then stained with hematoxylin-eosin (H&E). For HPV identification, in situ hybridization was carried out on formalin-fixed, paraffin-embedded, 4-μm tissue sections using standard technique and manufacturer's specifications. Wide spectrum probes for HPV-6, 11, 16, 18, 30, 31, 35, 45, 51, and 52 were used. Positive and negative controls were included in each assay. A cervicovaginal Pap smear was performed according to established protocol.

Biopsies of the right labium majus and left labium minus were performed, and results of histopathologic examination revealed scattered multinucleated cells in the basal to middle levels of squamous epithelium of a relatively normal-appearing epidermis (Figure 2); these findings were consistent with the diagnostic criteria for MAV. The multinucleated cells exhibited no significant cytologic atypia and had no evidence of "ground glass"–type nuclear changes. The number of nuclei varied from 2 to 8 per cell, and nuclei were similar in appearance to those within the surrounding keratinocytes. Nucleoli were prominent. Mild hyperkeratosis and chronic inflammation were present. No overt histologic evidence of VIN or condyloma acuminatum was identified. Results of in situ hybridization for HPV-6, 11, 16, 18, 30, 31, 35, 45, 51, and 52 revealed no staining for HPV (Figure 3). Results of a concurrent Pap smear revealed no atypical features.

Comment

MAV was first described in 1994 by McLachlin et al,[2] who reported on a series of 12 patients with vulvar lesions characterized by a unique histologic pattern of focal multinucleation in the basal to middle epithelial layers of the vulvar epidermis. In their study, as in this case, the histologic alterations ranged from single isolated multinucleated cells to clusters of such cells, sometimes with adjacent slight parakeratosis and mild nonspecific chronic inflammation. Multinucleated cells contained 2 to 10 nuclei, often with perinuclear clearing, reminiscent of that seen with HPV. The multinucleated squamous cells had a similar appearance to that of the adjacent mononuclear epithelial cells with minimal nuclear hyperchromasia and polymorphism. In 11 of their 12 reported cases, the initial histologic diagnosis was condyloma, atypia suggestive of condyloma, or VIN (grade 1). However, in all 12 cases, the classic histologic features of HPV infection were absent, and results of HPV DNA studies by polymerase chain reaction/restriction fragment length polymorphism analysis and in situ hybridization modalities failed to demonstrate the presence of HPV.

In the present case, the clinical presentation of flesh-colored, flat-topped, vulvar papules overlapped with features that may be seen in condyloma acuminatum, VIN, seborrheic keratosis, and lichen sclerosus et atrophicus. The differential diagnosis of

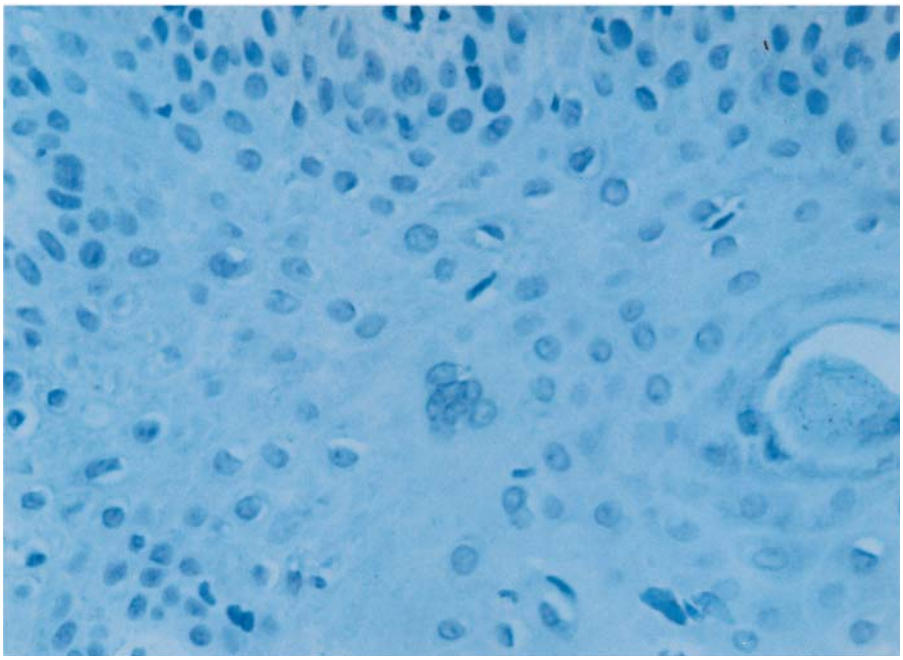

Figure 3. In situ hybridization for human papillomavirus (HPV) reveals absence of staining for the viral genome in the multinucleated cells or elsewhere in the squamous epithelium (immunohistochemical stain for wide spectrum HPV, original magnification ×40).

multinucleation in vulvar squamous epithelia includes herpetic lesions, inflammatory dermatoses, extramammary Paget disease, and nonspecific reactive changes. However, the most important differential entities are HPV-related lesions (condyloma and VIN), since the treatment and natural history of the HPV-related diseases appear to be different from those of MAV.

The pathogenesis and clinical significance of vulvar multinucleated atypia are unclear. Indeed, multinucleated squamous cells in the epidermis of inflammatory skin lesions, particularly pruritic ones, were described 20 years ago. It has been postulated that such multinucleated squamous cells represent a defect in nuclear division in persistently rubbed skin in both genital and extragenital locations.[3,4]

Our patient's long history of daily feminine pad usage and chronic vaginal infections suggested the possibility that an exaggerated response to topical irritation was the cause of MAV. The relationship of the current vulvar MAV to her remote history of cervical atypia was also uncertain but may have been entirely coincidental, given the relatively high frequency of cervical HPV in the general population, as well as the negative results of a concurrent cervicovaginal Pap smear. The immunonegativity for wide spectrum genital serotypes of HPV (6, 11, 16, 18, 30, 31, 35, 45, 51, and 52) or by in situ hybridization studies militated against papillomavirus as the cause of these lesions.

The possibility that MAV represents a squamous dysplastic process (VIN) must be considered, given the presence of multinucleated atypia involving the lower half of the vulvar epithelium. However, in the original report of 12 cases, vulvar biopsies were performed in 5 patients, either prior to or subsequent to the diagnosis of MAV, and none of the biopsy results demonstrated evidence of VIN or recurrent MAV.[2] Indeed, regular follow-up of patients with vulvar MAV is prudent until the uncertainties surrounding its etiology and natural history are clarified.

Recognizing the existence of MAV and its key features should enable dermatologists to differentiate this lesion from atypias associated with infectious agents (eg, HPV, herpes simplex virus) and intraepithelial dysplasias (eg, VIN), thereby contributing to appropriate therapeutic management.

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