

Grape Cells (Multinucleated Keratinocytes) in Noninfectious Dermatoses: Case Series and Review of the Literature

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Abstract: Multinucleated keratinocytes (also known as multinucleated epidermal giant cells) are a frequently overlooked histological finding in noninfectious inflammatory dermatoses. They are sometimes found in conditions characterized by chronic rubbing and pruritus, such as lichen simplex chronicus or prurigo nodularis, and may be a helpful clue in making the clinical diagnosis. This finding must be differentiated from other conditions characterized by multinucleated keratinocytes on histopathology, specifically herpes simplex, varicella zoster, or measles viral infections. The authors present a case series of 2 patients with unique clinical noninfectious diagnoses but similar histopathologic findings on biopsy. The histopathologic findings on both cases demonstrated multinucleated keratinocytes, which were related to manipulation of the epidermis.

Key Words: multinucleated keratinocytes, grape cells, lichen simplex chronicus, prurigo nodularis, factitial disorder, multinucleated atypia of the vulva

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CASES

Case 1 is a healthy 16-year-old white female with an 8-month history of tender, annular, erythematous, papules and plaques on the trunk and extremities. The first lesions appeared on the legs and hips, followed by the trunk. She denied preceding trauma or medication changes. Some of the areas became bullous. Serum studies for autoimmune blistering diseases were unremarkable. Complete blood count, complete metabolic panel, antineutrophil cytoplasmic antibodies, and antinuclear antibodies were within normal limits. Topical and oral corticosteroids and oral antibiotics were not helpful. Review of systems revealed no other complaints. Social history was significant for ongoing divorce and custody battle in her parents.

On physical examination, there were geometric tan patches on the abdomen and upper extremities with a noninflammatory border and central clearing. On the left medial lower leg, there was a linear array of annular tan patches with central clearing. There was an erythematous plaque on the right lateral dorsal foot (Fig. 1). Two

biopsies on the right lateral foot were performed—1 for direct immunofluorescence and 1 for hematoxylin and eosin stain. Direct immunofluorescence examination was negative. Hematoxylin and eosin-stained slides showed superficial epidermal necrosis, multinucleated keratinocytes at all levels of the epidermis, and a sparse superficial perivascular inflammatory infiltrate. The number of nuclei varied from 5 to 15 per cell. No viral changes were seen (Figs. 2 and 3). Immunohistochemistry stains for herpes simplex virus (HSV) 1, HSV 2, and varicella zoster virus were negative.

The patient's examination, pathologic findings, and history of simultaneous stressful life events led to the diagnosis of factitial disorder. When confronted, the patient denied any purposeful manipulation of her skin. She was lost to follow-up.

Case 2 is a 40-year-old gravida 3 para 1 white woman presented for evaluation of a white-appearing vulvar mucosal plaque noticed during routine gynecologic annual examination. She did not know how long the lesion was present, but she reported occasional mild pruritus in the area. It was not painful. She had a medical history of Hashimoto hypothyroidism. She did not have any history of a genital herpes infection.

On physical examination, there was an ill-defined lichenified white plaque localized to the inner aspect of the right labia minora (Fig. 4). There were no similar appearing lesions on the remainder of her mucocutaneous examination.

A shave biopsy was performed to rule out leukoplakia and lichen sclerosis. The biopsy showed prominent hyperkeratosis, hypergranulosis, and acanthosis in the epidermis. Focally, there were several multinucleated epidermal giant cells present in the lower third of the epidermis. The number of nuclei varied from 5 to 11 per cell. In the dermis, there was superficial dermal fibrosis with sparse inflammation. Sclerosis and hyalinization of dermal collagen was not identified (Figs. 5 and 6). Morphologic features of leukoplakia, vulvar intraepithelial neoplasia, condyloma acuminatum, lichen planus, and lichen sclerosis were not seen. HSV 1, HSV 2, and varicella zoster virus immunohistochemistry stains were negative. Periodic acid–Schiff stain did not demonstrate fungal elements.

The patient's history, examination, and histopathologic findings led to the diagnosis of lichen simplex chronicus with multinucleated atypia of the vulva. She used topical clobetasol 0.05% ointment daily for over 8 weeks with minimal results. The vulvar white plaque persisted.

DISCUSSION

Multinucleated keratinocytes are a characteristic pathologic finding in cutaneous viral infections with herpes simplex and varicella zoster¹ and measles.² They are also rarely reported in dyskeratotic dermatoses, such as lichen planus.³ Multinucleated keratinocytes with at least 3 clumped nuclei

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FIGURE 1. On the lateral aspect of the right dorsal foot, there is an edematous erythematous plaque with a slightly indurated superior border.

per cell were originally thought to be a rare histological finding resulting from inflammatory skin diseases, including contact dermatitis, pityriasis lichenoides chronica,⁴ and pityriasis rosea.⁵ Tagami and Uehara⁶ found that multinucleated keratinocytes were frequently found in pruritic and lichenified lesions, most commonly prurigo nodularis. More recently, multinucleated keratinocytes with up to 16 nuclei per cell were noted in a biopsy of a patient with factitial disorder.⁷

The pathogenesis behind the formation of these cells is not entirely clear. It has been hypothesized that these findings are a result of improper cell division secondary to malaligned keratinocyte tonofilaments.³ Other authors have suggested

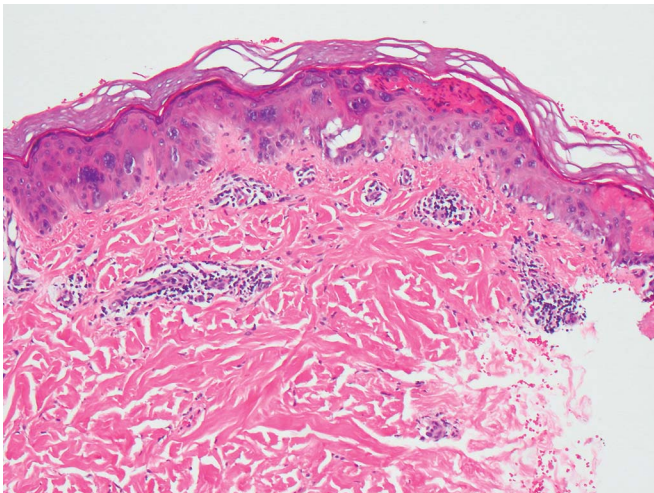


FIGURE 2. Multiple basophilic multinucleated keratinocytes occurring in the background of focal superficial epidermal necrosis and focal compact hyperkeratosis. There is a mild superficial perivascular lymphocytic infiltrate. These findings are consistent with external trauma to the skin. Hematoxylin and eosin stain on microscopic magnification of 10× high-power field.

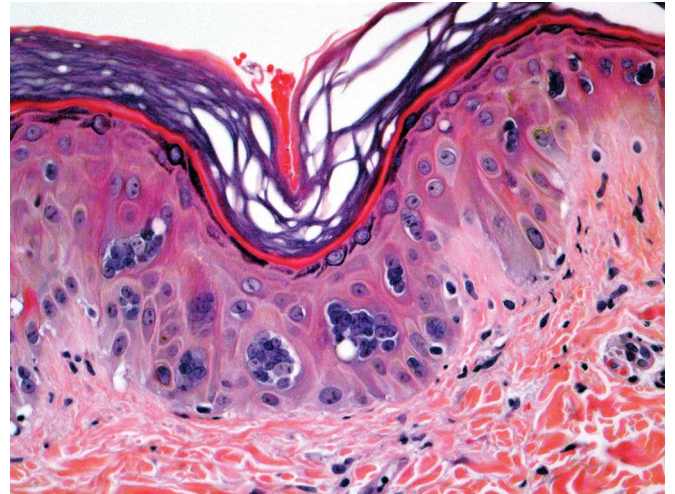


FIGURE 3. At the middle to lower third of the epidermis, there are multinucleated keratinocytes with grouped basophilic nuclei. The surrounding cytoplasm is more pale and hyalinized compared with nearby mononuclear keratinocytes. Hematoxylin and eosin stain on microscopic magnification of 40× high-power field.

that these results are from cell–cell fusion of adjacent keratinocytes rather than mitotic malfunction, as evidenced by a relative lack of expression in Ki-67, a marker of cell activity.⁷

Multinucleated atypia of the vulva is another non-infectious skin disease that may present with multinucleated keratinocytes. Multinucleated atypia of the vulva is a lesion of uncertain etiology that is theorized to relate to chronic mechanical irritation of vulvar skin. It was first described by McLachlin et al⁸ in a case series of 12 patients with biopsies demonstrating multinucleated keratinocytes with 2–10 nuclei in the basal and middle epithelial layers. No association with human papilloma virus infection was found by in situ hybridization or polymerase chain reaction. We find the name “multinucleated atypia of the vulva” misleading because McLachlin et al⁸ states that there is minimal cytological atypia and the multinucleated cells lacked nuclear hyperchromasia, irregularity, or pleomorphism. In addition, Rausch et al⁹ presented an isolated case with irritation and flat-topped papules on physical examination and similar findings of multinucleated keratinocytes on biopsy. The patient in this case had a history of daily feminine pad use and chronic vaginal infections, and her biopsy displayed mild hyperkeratosis with multinucleated atypia of the vulva,⁹ which is highly suggestive of chronic skin irritation. In situ hybridization for multiple human papilloma virus subtypes was also negative. It has been theorized that multinucleated atypia is not a unique condition but rather a histological finding associated with pruritus that can be found anywhere on the body.¹⁰ We believe that multinucleated atypia of the vulva may represent a variant of lichen simplex chronic or prurigo nodularis with multinucleated keratinocytes, which is located on vulvar skin.

Both of the patients in this case series demonstrated multinucleated keratinocytes related to chronic manipulation of the epidermis. Although the physical examination findings and diagnoses in these cases differed, the multinucleated



FIGURE 4. On the inner aspect of the right labia minora, there is an ill-defined lichenified white plaque.

keratinocytes on biopsy were suggestive of chronic rubbing or trauma as the etiology. In case 1, the biopsy findings were helpful in making the diagnosis of factitial disorder when the

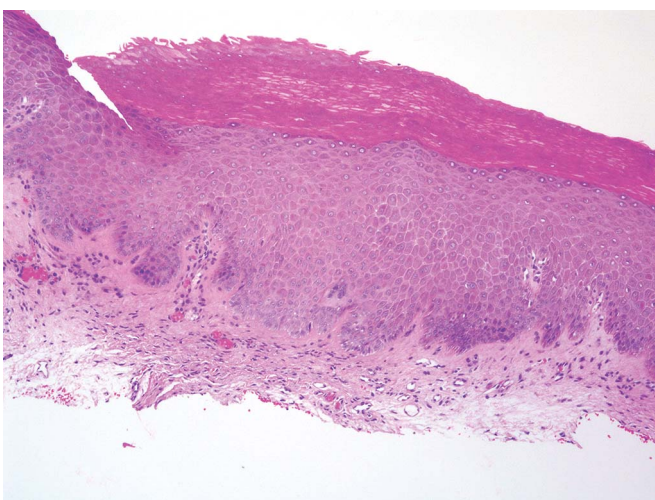


FIGURE 5. Vulvar skin with hyperkeratosis, hypergranulosis, and acanthosis. At the lower third of the epidermis, there is a focal area of multinucleated keratinocytes with closely grouped basophilic nuclei. Hematoxylin and eosin stain on microscopic magnification of 20× high-power field.

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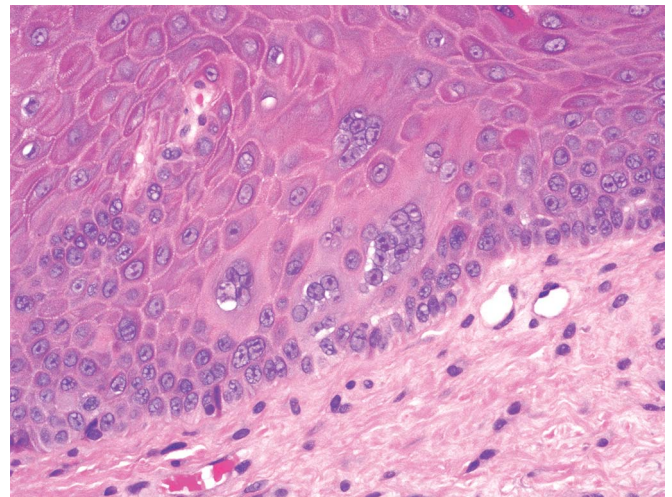


FIGURE 6. At the lower third of the epidermis, there are multinucleated keratinocytes with closely grouped basophilic nuclei. The surrounding cytoplasm is more pale and hyalinized compared with nearby mononuclear keratinocytes. Hematoxylin and eosin stain on microscopic magnification of 40× high-power field.

history was misleading. In case 2, the biopsy showed evidence of chronic rubbing (hyperkeratosis, hypergranulosis, acanthosis) and no findings of infection and no significant morphologic findings of neoplasia. This led to the diagnosis of lichen simplex chronicus with multinucleated atypia of the vulva.

It is important to note that these findings can also be seen in herpes viral infections, which should be ruled out in appropriate settings, especially in locations near mucosal surfaces. But in multinucleated keratinocytes from noninfectious inflammatory dermatoses, there are no findings suggestive of viral infections, such as nuclear viral inclusions, chromatin margination, or epidermal acantholysis.⁸

In summary, multinucleated keratinocytes (also known as multinucleated epidermal giant cells) are often overlooked but commonly found in noninfectious inflammatory dermatoses characterized by lichenification and pruritus. This may be a helpful histopathologic clue in making the clinical diagnosis. Multinucleated keratinocytes from noninfectious dermatoses, including multinucleated atypia of the vulva, typically have 3 or more closely grouped nuclei that appear more basophilic to purple color than normal mononuclear keratinocytes. The nuclei of multinucleated keratinocytes are round- to oval-shaped and are normal to slightly smaller size compared with nearby normal mononuclear epithelial cells. There is minimal nuclear hyperchromasia and minimal nuclear pleomorphism. The chromatin is more vesicular with a conspicuous but not significantly enlarged nucleoli. The cytoplasm of the multinucleated keratinocytes has more of a hyalinized pink color.⁶⁻⁸ Mitotic rate can be increased in multinucleated and mononuclear epithelial cells but not as significantly as seen in neoplastic processes.^{6,7} We propose the name “grape cells” for multinucleated keratinocytes because of their distinct histology that reminds us of a cluster of grapes. It is important to note that although this finding is indicative of external manipulation,

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any underlying inflammatory, infectious, or neoplastic processes should be excluded.

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