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Epidermal multinucleated giant cells are not always a histopathologic clue to a herpes virus infection: multinucleated epithelial giant cells in the epidermis of lesional skin biopsies from patients with acantholytic dermatoses can histologically mimic a herpes virus infection

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ABSTRACT

Background: Multinucleated giant cells in the epidermis can either be epithelial or histiocytic. Epithelial multinucleated giant cells are most often associated with herpes virus infections.

Purpose: To review the histologic differential diagnosis of conditions with epithelial and histiocytic multinucleated giant cells—since multinucleated giant cells in the epidermis are not always pathognomonic of a cutaneous herpes virus infection—and to summarize dermatoses in which herpes virus infection has been observed to coexist.

Methods: Two individuals with acantholytic dermatoses whose initial lesional skin biopsies showed multinucleated epithelial giant cells suggestive of a herpes virus infection are reported. Using the PubMed database, an extensive literature search was performed on multinucleated giant cell (and epidermis, epithelial, and histiocytic) and herpes virus infection. Relevant papers were reviewed to discover the skin conditions with either multinucleated giant cells in the epidermis or coincident cutaneous herpes virus infection.

Results: Initial skin biopsies from patients with either pemphigus vulgaris or transient acantholytic dermatosis mimicked herpes virus infection; however, laboratory studies and repeat biopsies established the correct diagnosis of their acantholytic dermatosis. Hence, epidermal multinucleated giant cells are not always a histopathologic clue to a herpes virus infection. Indeed, epithelial multinucleated giant cells in the epidermis can be observed not only in the presence of infection (herpes virus), but also acantholytic dermatoses and tumors (trichoepithelioma and pleomorphic basal cell carcinoma). Histiocytic multinucleated giant cells in the epidermis can be observed in patients with either giant cell lichenoid dermatitis or lichen nitidus of the palms. *(continued next page)*

ABSTRACT (continued)

Conclusions: Epithelial and histiocytic multinucleated giant cell can occur in the epidermis. Keratinocyte-derived multinucleated giant cells are most commonly associated with herpes virus infection; yet, they can also be observed in patients with skin tumors or acantholytic dermatoses. Cutaneous herpes simplex virus infection can coexist in association with other conditions such as acantholytic dermatoses, benign skin tumors, bullous disorders, hematologic malignancies, inflammatory dermatoses, and physical therapies. However, when a herpes virus infection is suspected based upon the discovery of epithelial multinucleated giant cells in the epidermis, but either the clinic presentation or lack of response to viral therapy or absence of confirmatory laboratory studies does not support the diagnosis of a viral infection, the possibility of a primary acantholytic dermatosis should be considered and additional lesional skin biopsies performed. Also, because hematoxylin and eosin staining is not the golden standard for confirmation of autoimmune bullous dermatoses, skin biopsies for direct immunofluorescence should be performed when a primary bullous dermatosis is suspected since the histopathology observed on hematoxylin and eosin stained sections can be misleading.

Introduction

Herpes virus infection of the skin is characterized by the finding of multinucleated giant cells in the epidermis. We report two individuals with acantholytic dermatoses whose initial lesional skin biopsies showed multinucleated epithelial giant cells suggestive of a herpes virus infection; however, all viral studies were negative and subsequent biopsies of their lesions demonstrated pathognomonic features of either pemphigus vulgaris or transient acantholytic dermatosis. The histologic differential diagnosis of conditions with multinucleated giant cells in the epidermis is reviewed and dermatoses in which herpes virus infection has been observed to coexist are summarized.

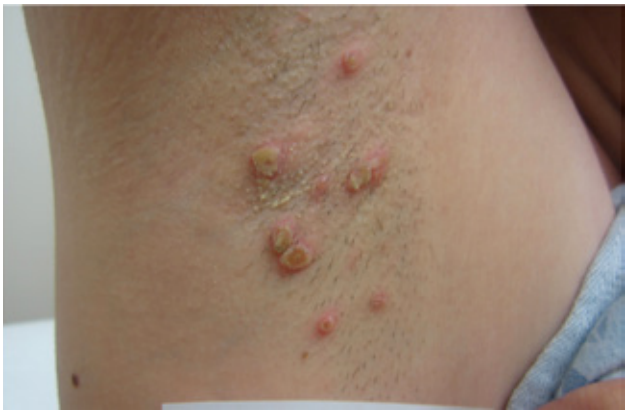


Figure 1. The right axilla of a woman with pemphigus vulgaris shows pustules and vesicles on a faint erythematous base. (Copyright: ©2014 Cohen et al.)

Case reports

Case 1

A 24-year-old Caucasian woman presented with painful oral sores that persisted after a short tapering course of oral corticosteroids (methylprednisolone dose pack) that was stopped after 5 days. Her past medical history was significant for type 1 diabetes mellitus and genital herpes simplex virus infection. She subsequently developed tender fluid-filled blisters of her axilla and groin and was empirically treated with oral valacyclovir 1000 mg twice daily without improvement.

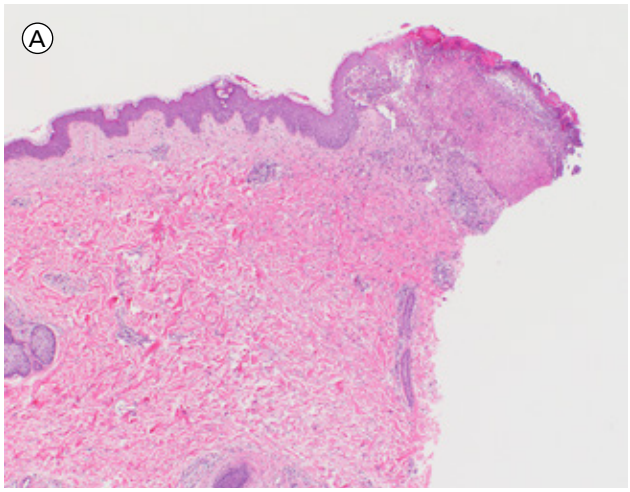
Examination of the oral cavity showed ulcers on the hard palate, the buccal mucosa and the mucosa of the gingiva and labia. Pustules, vesicles, and bullae were observed within the right axillae (Figure 1) and the labia majora. A lesional skin biopsy from the right axilla was performed; specimens for bacterial culture, direct fluorescent antibody studies and viral cultures were also obtained.

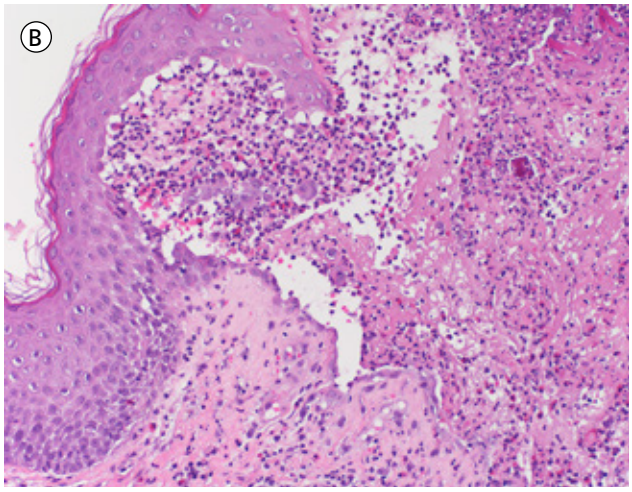
Microscopic examination showed epidermal necrosis and ulceration surmounted by basophilic debris; rare cocci-shaped bacteria were seen within the inflammatory scale crust. Focal reticular degeneration, intraepidermal neutrophilic pustules forming a suprabasilar cleft, and numerous multinucleated keratinocyte giant cells demonstrating nuclear molding were noted. There was a perivascular infiltrate in the upper dermis consisting of neutrophils and eosinophils (Figure 2).

The pathology was consistent with a herpes virus infection. The patient was hospitalized and treated for disseminated herpes virus infection with intravenous acyclovir at a dose of 10 mg per kilogram every 8 hours. The bacterial culture grew methicillin-resistant Staphylococcus aureus and intravenous vancomycin was added.

She continued to develop similar-appearing new lesions not only in her mouth, axilla and groin, but also on her arms and abdomen; in addition, earlier pustules and vesicles had enlarged and/or ruptured (Figure 3). The direct fluorescence antibody studies and the viral cultures were negative for both herpes simplex virus and varicella-zoster virus. Repeat skin biopsies were performed for routine staining and direct immunofluorescence.

Microscopic examination showed an intraepidermal blister containing acantholytic keratinocytes, numerous eosinophils, and occasional neutrophils; the adjacent epithelium showed spongiosis with eosinophils. Perivascular inflammation, consisting of prominent eosinophils and occasional lym-





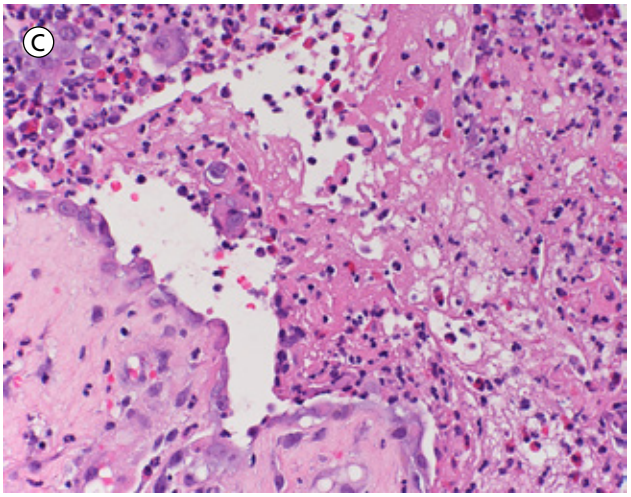


Figure 2. (A) Distant, (B) close and (C) closer views of the initial biopsy specimen that showed features consistent with a herpes virus infection. (A) Basophilic debris is seen within the inflammatory scale crust overlying necrosis and ulceration of the epidermis. (B) There is a suprabasilar cleft showing an intraepidermal neutrophilic pustule; multinucleated keratinocyte giant cells are noted in the pustule. (C) Nuclear molding can also be noted within several of the multinucleated keratinocyte giant cells (hematoxylin and eosin; a= x4, b=20, c=x40). (Copyright: ©2014 Cohen et al.)

phocytes, was present in the upper dermis (Figure 4). Direct immunofluorescence showed positive intercellular staining in the epidermis for IgG and C3. Subsequently, enzyme-linked immunosorbent assay (ELISA) testing demonstrated that the serum IgG titers were elevated for both desmoglein 1 and desmoglein 3.

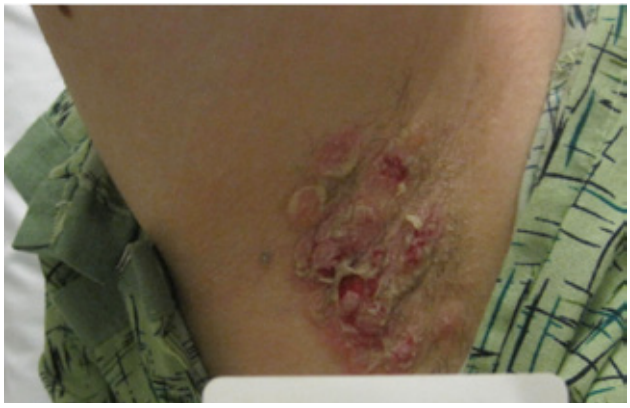
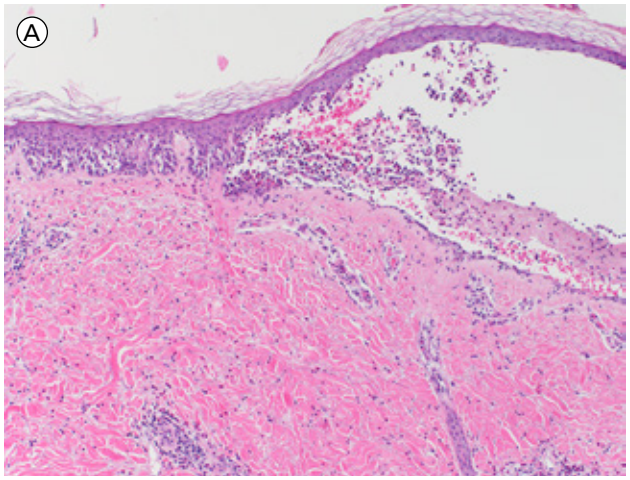


Figure 3. Enlargement and/or rupture of pustules and vesicles in the right axilla of the women with pemphigus vulgaris. (Copyright: ©2014 Cohen et al.)



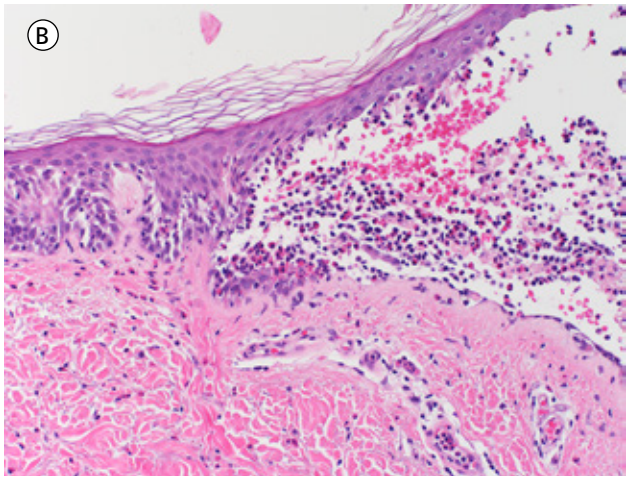
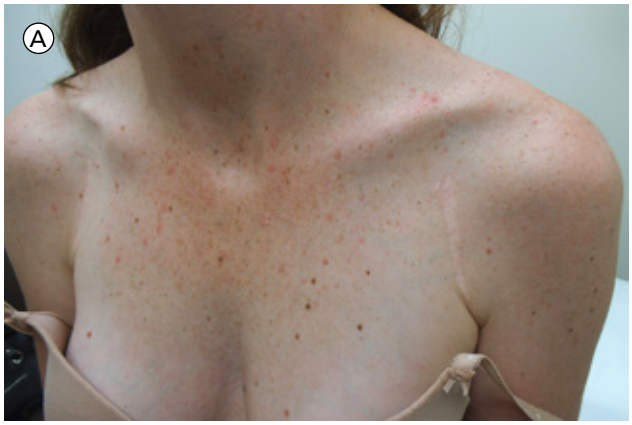
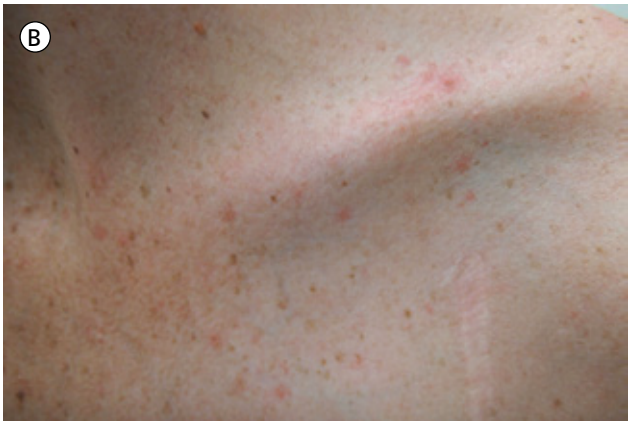


Figure 4. (A) Distant and (B) closer views of the repeat biopsy specimen that establish the diagnosis of pemphigus vulgaris. Acantholytic keratinocytes, numerous eosinophils, and occasional neutrophils are present in an intraepidermal blister; eosinophilic spongiosis is present in the adjacent epithelium. Prominent eosinophils and occasional lymphocytes compose the perivascular infiltrate in the upper dermis (hematoxylin and eosin; a= x20, b=x40). (Copyright: ©2014 Cohen et al.)





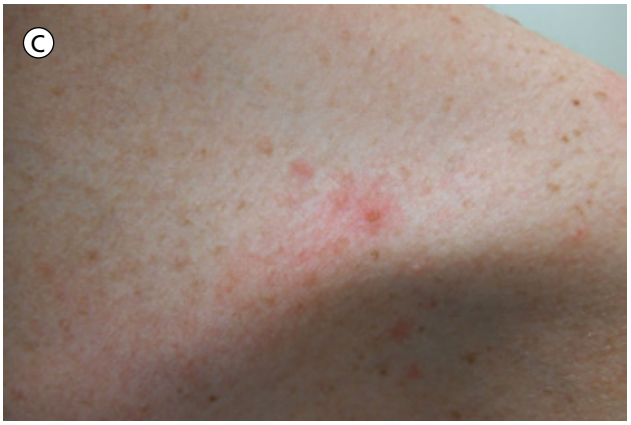


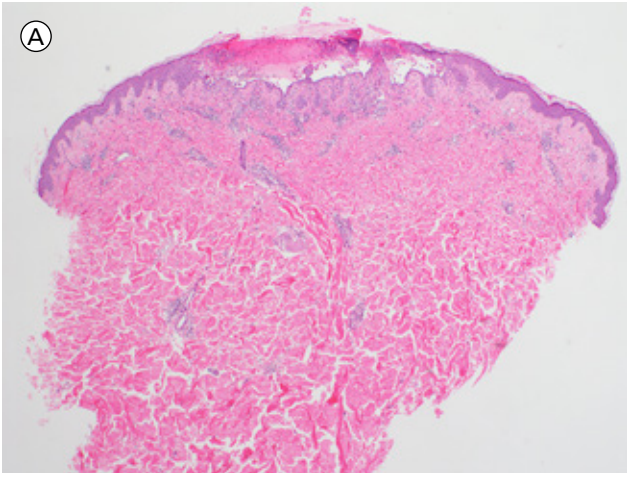
Figure 5. (A) Distant, (B) close and (C) closer view of the left upper chest of a woman with transient acantholytic dermatosis presenting as pruritic erythematous papules. (Copyright: ©2014 Cohen et al.)

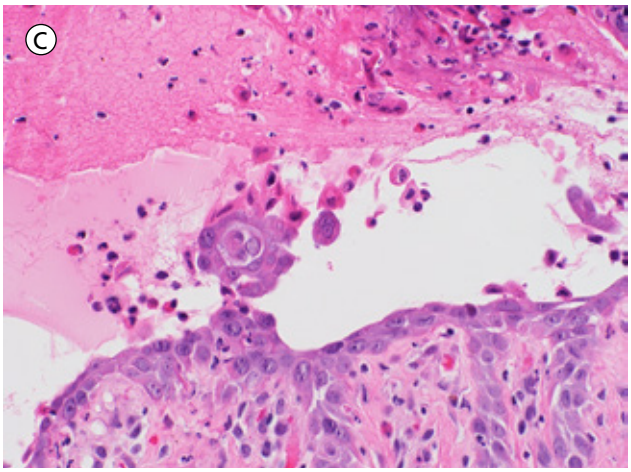
Correlation of the clinical findings, laboratory studies, and repeat skin biopsies established a diagnosis of pemphigus vulgaris. Initial management included 60 mg daily of oral prednisone. She also received intravenous rituximab, 2 doses of 1000 mg each separated by 2 weeks, prior to tapering her daily prednisone over the next 6 months. Her skin lesions resolved without recurrence.

Case 2

A healthy 40-year-old Caucasian woman presented with a recurrent itchy rash on her chest and abdomen of more than one-year duration. Her past medical history was negative for herpes virus infection.

Cutaneous examination revealed discrete pruritic erythematous and crusted papules on her chest and abdomen (Figure 5). A lesional biopsy was performed. Empiric topical treatment was initiated with triamcinolone 0.1% ointment.





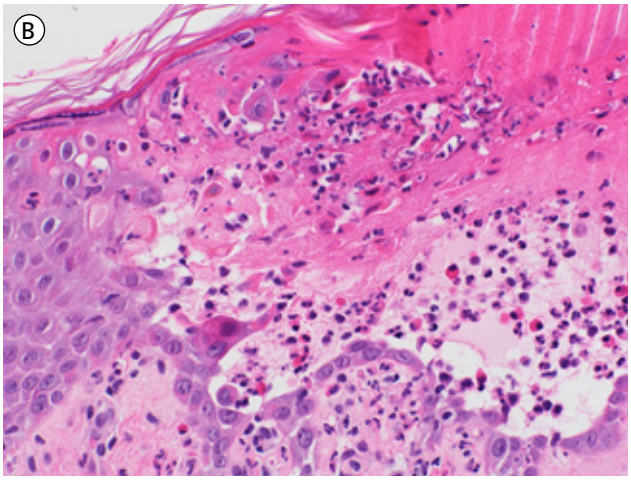
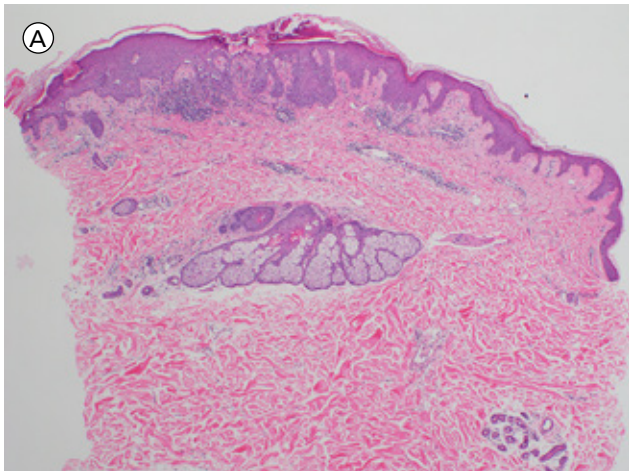
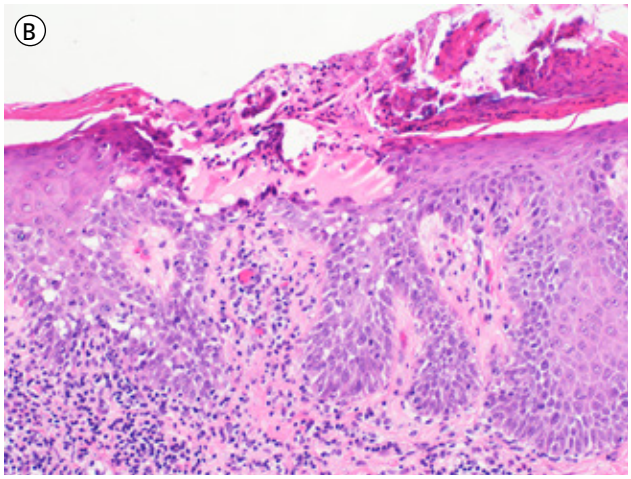


Figure 6. (A) Distant, (B) close and (C) closer views of the initial biopsy specimen that showed features consistent with a herpes virus infection. (A) An intraepidermal vesicle with suprabasilar epidermal acantholysis and cleft formation is noted. (B and C) Closer views show neutrophils and eosinophils in both the intraepidermal vesicle and the dermis; in the blister cavity, multinucleated keratinocyte giant cells with nuclear molding are also noted (hematoxylin and eosin; a= x4, b=x20, c=x40). (Copyright: ©2014 Cohen et al.)





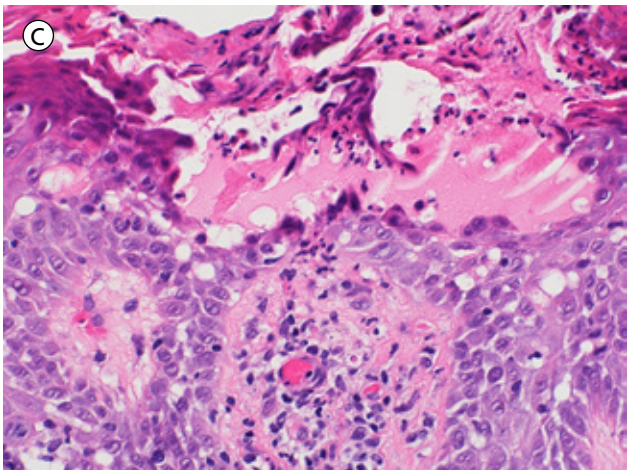


Figure 7. (A) Distant, (B) close and (C) closer views of the repeat biopsy specimen that establish the diagnosis of transient acantholytic dermatosis. Acanthosis, with focal acantholysis and dyskeratosis, is noted in the epidermis and lymphocytic inflammation is present in the upper dermis; viral cytopathic changes are absent (hematoxylin and eosin; a= x4, b=x20, c=x40). (Copyright: ©2014 Cohen et al.)

Microscopic examination showed suprabasilar epidermal acantholysis and cleft formation with neutrophils and eosinophils in both the intraepidermal vesicle and the dermis. Multinucleated keratinocyte giant cells with nuclear molding were also seen in the blister cavity (Figure 6). The pathologic findings were interpreted as a herpes virus infection.

The clinical features and improvement with topical corticosteroid therapy did not correlate with the observed pathologic findings. Direct fluorescence antibody studies and viral cultures did not demonstrate herpes virus infection. A repeat skin biopsy was performed of a new lesion on her upper chest.

The second biopsy specimen showed acanthosis with focal acantholysis and dyskeratosis; viral cytopathic changes were absent. Lymphocytic inflammation was present in the upper dermis (Figure 7). Correlation of the clinical presentation, laboratory studies, and pathologic changes established the diagnosis of transient acantholytic dyskeratosis (Grover's disease).

Discussion

Multinucleated giant cells can be observed in the epidermis (Table 1) [1-10]. The etiology of the giant cells can either be epithelial or histiocytic. Histiocytic epidermal multinucleated giant cells have been noted in giant cell lichenoid dermatitis [7,8] and lichen nitidus of the palms [9,10].

TABLE 1. Conditions with multinucleated giant cells in the epidermis

Epithelial cell origin
Acantholytic dermatosis
Pemphigus vulgaris [current report]
Transient acantholytic dermatosis [current report]
Infection
Herpes virus infection [1-3]
Tumors
Benign
Trichoepithelioma [4]
Malignant
Pleomorphic basal cell carcinoma [5,6]
Histiocytic cell origin
Giant cell lichenoid dermatitis [7,8]
Lichen nitidus of the palms [9,10]

Epithelial multinucleated giant cells are most often associated with herpes virus infections [1-3]. However, they occasionally occur in either benign or malignant tumors of epidermal cell origin such as trichoepitheliomas or basal cell carcinomas, respectively [4-6]. We recently observed multinucleated giant cells of keratinocyte origin, which mimicked those noted in herpes virus infection, in the epidermis of patients with acantholytic dermatoses: pemphigus vulgaris [11-15] and transient acantholytic dermatosis [16-21].

Herpes virus infections of the skin usually present as erythematous-based vesicles. Microscopic examination of a

TABLE 2. Acantholytic or bullous dermatoses in which herpes simplex virus infection has been demonstrated to be present in the skin lesion [27-33]

Bullous pemphigoid
Epidermolysis bullosa
Familial benign chronic pemphigus (Hailey-Hailey disease)
Keratosis follicularis (Darier's disease)
Pemphigus foliaceus
Pemphigus vulgaris
Staphylococcus scalded skin syndrome
Transient acantholytic dermatosis (Grover's disease)

lesional biopsy often shows multinucleated ballooned keratinocyte giant cells in the epidermis containing steel-gray nuclei with accentuation of nucleoplasm at their periphery; acantholytic, sometime necrotic, keratinocytes within intraepidermal blisters can also be noted. The diagnosis of herpes virus infection can be confirmed by direct fluorescent antibody testing or viral culture [1-3,22-25].

Herpes simplex virus infection can coexist in association with other skin conditions; this likely represents the coincident development of this viral infection in an immunocompromised district—an area of skin that have been made vulnerable by a previous or concurrent cutaneous disorder [26]. In addition to acantholytic dermatoses and bullous disorders (Table 2) [27-33], herpes simplex virus can also occur in association with hematologic malignancies [27,34,35], inflammatory dermatoses [27,35], and physical therapies [27,35,36]. Rarely, herpes virus infection has been discovered in benign skin tumors, such as seborrheic keratoses [37].

Our patients had acantholytic dermatoses that were initially interpreted to represent a herpes virus infection based on the presence of multinucleated epithelial giant cells in the epidermis of lesional skin biopsies. However, additional evaluation (including direct fluorescent antibody studies and viral cultures) was negative for a viral infection. In addition, one patient failed to improve after oral or intravenous treatment with antiviral therapy. Subsequently, repeat biopsies for direct immunofluorescence and/or routine histology established the correct diagnosis for both patients.

Conclusion

Epithelial and histiocytic multinucleated giant cell can occasionally be found in the epidermis. Although keratinocyte-derived multinucleated giant cells are most commonly caused by a herpes virus infection, they can also be observed in either benign or malignant skin tumors or in patients with acantholytic dermatoses. Indeed, our patients presented with vesicular skin lesions that showed epidermal multinucleated giant cells on their initial biopsy specimens and were initially interpreted to represent a herpes virus infection. However, direct fluorescent antibody and culture studies did not confirm the diagnosis of a viral infection. Subsequently, repeat lesional skin biopsies revealed pathologic features that were able to establish the correct diagnosis of either pemphigus vulgaris or transient acantholytic dermatosis. Therefore, when a herpes virus infection is suspected based upon the discovery of epithelial multinucleated giant cells in the epidermis, but either the clinic presentation or lack of response to viral therapy or absence of confirmatory laboratory studies does not support the diagnosis of a viral infection, the possibility of a primary acantholytic dermatosis should be considered and additional lesional skin biopsies performed. Also, because hematoxylin and eosin staining is not the golden standard for confirmation of autoimmune bullous dermatoses, skin biopsies for direct immunofluorescence should be performed when a primary bullous dermatosis is suspected since the histopathology observed on hematoxylin and eosin stained sections can be misleading.

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