Incidental Cutaneous Reaction Patterns: Epidermolytic Hyperkeratosis, Acantholytic Dyskeratosis, and Hailey-Hailey-Like Acantholysis: A Potential Marker of Premalignant Skin Change

Erich M. Gaertner

SaraPath Diagnostics, 2001 Webber Street, Sarasota, FL 34239, USA

Correspondence should be addressed to Erich M. Gaertner, dermpathdoc@msn.com

Received 8 December 2010; Accepted 28 January 2011

Focal acantholytic dyskeratosis (FAD), epidermolytic hyperkeratosis (EHK), and Hailey-Hailey-like acantholysis (HH) represent unique histology reaction patterns, which can be associated with defined phenotypic and genotypic alterations. Incidental microscopic foci demonstrating these patterns have been identified in skin and mucosal specimens in association with a gamut of disease processes. These changes, when secondary, are of unclear etiology and significance. The following study further analyzes the incidence and association of these histologic patterns in a routine pathology/dermatopathology practice.

1. Introduction

A variety of incidental microscopic cutaneous changes have been described in skin and mucosal specimens. Whether these represent spurious changes of no consequence, or true manifestations of underlying cellular alterations, remains unclear. Incidental FAD, HH, and EHK have been reported in association with a wide variety of benign and malignant skin conditions. (Table 2) Some authors believe these changes represent markers for underlying widespread cellular damage, likely from prolonged sun/ultraviolet light exposure. Several studies show an association of these changes with preneoplastic lesions and malignancy, supporting this theory. However, others cite a variety of clinical and pathologic evidence to refute this. A potential association between EHK, and possibly FAD, with atypical/dysplastic nevus has also been reported, although not uniformly.

2. Material and Methods

247 consecutive skin specimens covering a three-month period (1/04-3/04) were reviewed by the author to identify incidental foci of Hailey-Hailey-like acantholysis (HH) and focal acantholytic dyskeratosis (FAD). Subsequently, 500 consecutive skin specimens were reviewed by the author (8/08-9/08) at a different institution to evaluate for incidental foci of epidermolytic hyperkeratosis (EHK). An incidental focus was defined as a minor histologic finding occurring within a biopsy or excision specimen demonstrating a separate, primary process. All cases in which these patterns comprised the primary process were excluded. HH, FAD, and EHK patterns were defined utilizing standard diagnostic criteria. (Table 1) All cases were formalin fixed, paraffin embedded, and hematoxylin and eosin stained as per standard protocol.

3. Results

Six cases of incidental FAD and HH were identified in the 247 skin specimens reviewed, representing 2.4% of the total reviewed. Of the six cases, three were shave biopsies (chest, back, and face), two were excisions (back, face), and one was a punch biopsy (scalp). Three specimens had an HH-like pattern (1.2% of total), and three had an FAD pattern. Four patients were male and two were female. The average patient age was 68 years (range 41–86). Three cases
were associated with malignant or premalignant epidermal neoplasia: basal cell carcinoma (HH), actinic keratosis (HH), and melanoma in situ (FAD) (Figure 3). Two were associated with significant inflammation: inflamed seborrheic keratosis (HH) and bullous lichen planus (FAD) (Figure 4). One biopsy was of lichen simplex chronicus (FAD) (Figure 2). The average diameter of acantholysis was 0.3 mm, with a range of 0.1 mm to 0.5 mm. Four cases were associated with prominent solar elastosis.

Nine cases of EHK were identified in the 500 skin specimens reviewed, representing 1.8% of total. Of the nine cases, six were excisions (arm, cheek, back [9], and neck [9]), and three were shave biopsies (thigh and back [9]). Four patients were male and five were female. The average patient age was 68 years (range 54–85). Six cases were associated with excisions of epidermal malignancies: basal cell carcinoma [16], squamous cell carcinoma [9], and melanoma in situ [7]. Three cases were associated with biopsies of dysplastic/Clark's nevi (out of a total of 82 dysplastic nevi diagnosed during this period) (Figure 1). The average diameter of EHK was 0.15 mm, with a range of 0.05 mm to 0.8 mm. Six cases were associated with prominent solar elastosis. None were associated with significant inflammation.

### Table 1

| Diagnosis                        | Histology                                                                 |
|----------------------------------|---------------------------------------------------------------------------|
| Epidermolytic hyperkeratosis     | Perinuclear vacuolization of keratinocytes in the upper epidermis, irregular keratohyaline granules, and compact hyperkeratosis |
| Focal acantholytic dyskeratosis  | Acantholysis and dyskeratosis at all levels of the epidermis, suprabasal clefting, hyperkeratosis, and parakeratosis |
| Hailey-Hailey-like acantholysis  | Prominent acantholysis at all epidermal levels with epidermal hyperplasia and often suprabasal clefting |

4. Discussion

Several previous studies have reviewed incidental foci of FAD, HH, or EHK. In the largest studies, incidental acantholysis was identified in 14 of 9000 specimens [35], and incidental FAD was identified in 8 of 5800 skin specimens [21]. Incidental EHK was identified in 21 out of approximately 30,000 specimens [1] and 41 out of 21,176 consecutive specimens [34]. In another study, these incidental reaction patterns were identified in 2.6% of the 1606 reviewed skin specimens, with incidental FAD identified in 0.44% (7 cases), EHK in 1.2% (19 cases), and HH in 0.68% (11 cases) [20]. The reported age of affected patients ranged from 3 to 87 years, with the largest study yielding a mean age of 55 years for FAD and 45 years for EHK. (8,25) There is no reported significant sex difference for incidental FAD or HH patterns, but incidental EHK was twice as common in men than women in the largest study [1].

These foci occur in both sun-exposed and sun-protected areas, with occurrence on the trunk more common than the head/neck or extremities. The involved areas are generally quite small, often involving only a single rete ridge, although have been reported as large as 12 mm [21]. They generally occurred in clinically normal skin adjacent to the primary lesion although they can occur within the lesion. Occasionally, these patterns are combined in a single specimen, and foci of acantholysis with overlapping histologic patterns have been described. Other reported incidental acantholytic patterns include those with features of pemphigus vulgaris and superficial pemphigus [35].

The etiology of these changes is unclear. Incidental FAD, HH, and EHK have been previously associated with premalignant and malignant lesions. This was also noted in the current study, with incidental FAD and HH showing a 50% association (3 of 6 cases), and EHK showing a 100% association (9 of 9 cases if one includes dysplastic nevus in this category). Of note, 3 of 9 cases of incidental EHK were associated with dysplastic nevus. A total of 82 dysplastic nevi were diagnosed during the study, yielding a low sensitivity of 3.7% for EHK as a marker for dysplastic nevi, although of a high specificity, given no cases were identified in ordinary nevi.

Incidental EHK has been reported to be a useful marker when present for dysplastic nevus, being found more commonly in or around nevi with architectural disorder than in common melanocytic nevi [5]. This was confirmed in a
Table 2: Conditions reported in association with described incidental reaction patterns.

| Condition                                      |
|------------------------------------------------|
| **Epidermal hyperkeratosis**                   |
| Acanthoma [1], acrosyringeal epidermolytic papulosis neviformis [2], actinic keratosis [1, 3], atypical/dysplastic nevus [4–6]*, basal cell carcinoma [1, 3]*, epidermoid cyst [3], infundibular cyst [7], dilated hair follicle [4], dilated pore [8], drug-induced acne [9], epidermal nevus [1, 3], granuloma annulare [10], hair follicle [1], hidradenoma [3], intraepidermal sweat duct unit [3], junctional/compound melanocytic nevus [1, 4–6], leukoplakia [11, 12], lichen amyloidosis [10], melanoma [1, 13]*, nevus comedonicus [14, 15], normal oral mucosa [16], nummular eczema [3], reactive erythema [1], scar [1, 3], seborrheic keratosis [1, 10], squamous cell carcinoma [10, 17]*, systemic sclerosis [18], tattoo [1], trichilemmal cyst [10] |
| **Focal acantholytic dyskeratosis**            |
| Basal cell carcinoma [19], chondrodermatitis nodularis helicis [19], benign nevi [19, 20], bullous lichen planus [*], condyloma [21, 22], lichen simplex chronicus [*], comedone [19], dermatofibroma [19, 23], fibrous papule [24], hemorrhoids [25, 26], malignant melanoma [19, 20, 27]*, melanocytic nevus with architectural disorder, scars, ruptured follicle, seborrheic keratoses [4, 19, 20, 22], pityriasis rosea [28], pityriasis rubra pilaris [29–31], psoriasis [24, 28], scar [20], squamous cell carcinoma [17], trichofolliculoma [32, 33], vascular nevi/cutis marmorata telangiectasia congenital, vascular twin nevi [34] |
| **Hailey-Hailey-like acantholysis**           |
| Acral arteriovenous hemangioma, psoriasis, regressing keratoacanthoma, [35], condyloma acuminatum [28], actinic keratosis [*], basal cell carcinoma [*], benign tumors, malignant tumors [2], seborrheic keratosis [*] |

* Current report.

Figure 3: Incidental focal acantholytic dyskeratosis associated with prominent solar elastosis. This occurred in association with an excision of a melanoma in situ. (400X magnification, hematoxylin, and eosin stain).

Figure 4: Incidental focus of Hailey-Hailey-like acantholysis, occurring in association with a benign keratosis with features of seborrheic keratosis. (200X magnification, hematoxylin, and eosin stain).

...
incidental foci although they have not been well studied. As in previous studies, the foci of reported incidental FAD, HH, and EHK were quite small (0.3 mm for FAD/HH and 0.15 for EHK). Most of them were found in uninvolved skin adjacent to the primary lesion, but some were found within the lesion proper. Several of the primary disease processes in the current series have not been previously reported in association with incidental acantholysis (FAD and HH), such as bullous lichen planus.

Incidental FAD, HH, and EHK are interesting, uncommon cutaneous changes of unclear etiology and significance. In the current paper, these foci were associated with epidermal neoplasia, solar change, and inflammation. An association with premalignant change and malignancy has been previously reported, although not uniformly. An association between dysplastic nevi and incidental EHK and FAD has also been noted and may be of limited diagnostic utility. The exact etiology of these secondary patterns is unclear, but their presence may reflect more widespread, subclinical cutaneous injury.

Statement of Financial Interest

No competing financial interest exists. The research received no specific grant from a funding agency in the public, commercial, or not-for-profit sectors.

References

[1] P. Mahaisavariya, P. R. Cohen, and R. P. Rapini, “Incidental epidermolytic hyperkeratosis,” American Journal of Dermatopathology, vol. 17, no. 1, pp. 23–28, 1995.
[2] A. M. Zina, S. Bundino, and M. G. Pippione, “Acrosyringial epidermolytic papulosis neviformis,” Dermatologica, vol. 171, no. 2, pp. 122–125, 1985.
[3] A. H. Mehregan, “Epidermolytic hyperkeratosis. Incidental findings in the epidermis and in the intraepidermal eccrine sweat duct units,” Journal of Cutaneous Pathology, vol. 5, no. 2, pp. 76–80, 1978.
[4] A. C. S. Hutcheson, P. J. Nierert, and J. C. Maize, “Incidental epidermolytic hyperkeratosis and focal acantholytic dyskeratosis in common acquired melanocytic nevi and atypical melanocytic lesions,” Journal of the American Academy of Dermatology, vol. 50, no. 3, pp. 388–390, 2004.
[5] B. T. Williams and R. J. Barr, “Epidermolytic hyperkeratosis in nevi: a possible marker for atypia,” American Journal of Dermatopathology, vol. 18, no. 2, pp. 156–158, 1996.
[6] P. A. Conlin and R. P. Rapini, “Epidermolytic hyperkeratosis associated with melanocytic nevi: a report of 53 cases,” American Journal of Dermatopathology, vol. 24, no. 1, pp. 23–25, 2002.
[7] C. L. Steele, C. R. Shea, and V. Petronic-Rosic, “Epidermolytic hyperkeratosis within infundibular cysts,” Journal of Cutaneous Pathology, vol. 34, no. 4, pp. 360–362, 2007.
[8] A. B. Ackerman, “Histopathologic concept of epidermolytic hyperkeratosis,” Archives of Dermatology, vol. 102, no. 3, pp. 253–259, 1970.
[9] S. J. Lee, Y. Jang, D. Kim, G. Na, and W. Lee, “Epidermolytic hyperkeratosis as an incidental finding in drug-induced acne,” Journal of Dermatology, vol. 32, no. 8, pp. 686–687, 2005.
[10] C. L. Steele, C. R. Shea, and V. Petronic-Rosic, “Epidermolytic hyperkeratosis within infundibular cysts,” Journal of Cutaneous Pathology, vol. 34, no. 4, pp. 360–362, 2007.
[11] Y. Tokura, M. Takigawa, and M. Yamada, “Epidermolytic hyperkeratosis associated with a dilated pore,” Journal of Dermatology, vol. 14, no. 3, pp. 286–288, 1987.
[12] F. Vakilzadeh and R. Happle, “Epidermolytic leukoplakia,” Journal of Cutaneous Pathology, vol. 9, no. 4, pp. 267–270, 1982.
[13] L. Requena, C. Schoendorff, and E. Sanchez Yus, “Hereditary epidermolytic palmo-plantar keratoderma (Vorner type)—report of a family and review of the literature,” Clinical and Experimental Dermatology, vol. 16, no. 5, pp. 383–388, 1991.
[14] F. G. Aloisi and A. Molinero, “Nevus comedonicus with epidermolytic hyperkeratosis,” Dermatologia, vol. 174, no. 3, pp. 140–143, 1987.
[15] S. Barsky, J. A. Doyle, and R. K. Winkelmann, “Nevus comedonicus with epidermolytic hyperkeratosis. A report of four cases,” Archives of Dermatology, vol. 117, no. 2, pp. 86–88, 1981.
[16] D. K. Goette and N. A. Lapins, “Epidermolytic hyperkeratosis as an incidental finding in normal oral mucosa. Report of two cases,” Journal of the American Academy of Dermatology, vol. 10, no. 2, part 1, pp. 246–249, 1984.
[17] G. Brodsky, “Focal acantholytic dyskeratosis and epidermolytic hyperkeratosis of the oral mucosa adjacent to squamous cell carcinoma,” Oral Surgery Oral Medicine Oral Pathology, vol. 59, no. 4, pp. 388–393, 1985.
[18] T. Sasaki and H. Nakajima, “Incidental epidermolytic hyperkeratosis in progressive systemic sclerosis,” Journal of Dermatology, vol. 20, no. 3, pp. 178–179, 1993.
[19] G. Urmacher and M. H. Shiu, “Malignant melanoma in association with keratosis palmaris et plantaris (epidermolytic hyperkeratosis variant),” American Journal of Dermatopathology, vol. 7, pp. 187–190, 1985.
[20] J. A. Carlson, D. Scott, J. Wharton, and S. Sell, “Incidental histopathologic patterns: possible evidence of ‘field cancerization’ surrounding skin tumors,” American Journal of Dermatopathology, vol. 23, no. 5, pp. 494–496, 2001.
[21] D. J. M. DiMaio and P. R. Cohen, “Incidental focal acantholytic dyskeratosis,” Journal of the American Academy of Dermatology, vol. 38, no. 2, pp. 243–247, 1998.
[22] R. V. Kolbusz and D. F. Fretzin, “Focal acantholytic dyskeratosis in condyoma acuminata,” Journal of Cutaneous Pathology, vol. 16, no. 1, pp. 44–47, 1989.
[23] G. Kolde and F. Vakilzadeh, “Leukoplakia of the prepuce with epidermolytic hyperkeratosis: a case report,” Acta Dermato-Venereologica, vol. 63, no. 6, pp. 571–573, 1983.
[24] P. B. Googe, S. J. Chung, J. Simmons, and R. King, “Giant-sized condyloma of the breast with focal acantholytic changes,” Journal of Cutaneous Pathology, vol. 27, no. 6, pp. 319–322, 2000.
[25] G. F. Kao and V. I. Sulica, “Focal acantholytic dyskeratosis occurring in pityriasis rubra pilaris,” American Journal of Dermatopathology, vol. 11, no. 2, pp. 172–176, 1989.
[26] W. D. Hoover and J. C. Maize, “Focal acantholytic dyskeratosis occurring in pityriasis rubra pilaris,” American Journal of Dermatopathology, vol. 12, no. 3, pp. 321–323, 1990.
[27] C. B. Tannenbaum, R. C. Billick, and H. Srulovitz, “Multiple cutaneous malignancies in a patient with pityriasis rubra pilaris and focal acantholytic dyskeratosis,” Journal of the American Academy of Dermatology, vol. 35, no. 5, pp. 781–782, 1996.
[28] E. L. Garcia Silva, “Dysqueratose acantolitica focal em verruca seborreica,” *Medicina Cutanea Ibero-Latino-Americana*, vol. 8, no. 4–6, pp. 125–128, 1980.

[29] G. Rodsky, “Focal acantholytic dyskeratosis and epidermolytic hyperkeratosis of the oral mucosa adjacent to squamous cell carcinoma,” *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology*, vol. 59, pp. 388–393, 1985.

[30] M. L. Cintra and E. M. de Souza, “Focal acantholytic dyskeratosis: a snare for the pathologist. Report of two cases associated to psoriasis and fibrous papule of the nose,” *Revista Paulista de Medicina*, vol. 110, no. 5, pp. 237–240, 1992.

[31] J. K. Stern, J. E. Wolf, and T. Rosen, “Focal acantholytic dyskeratosis in pityriasis rosea,” *Archives of Dermatology*, vol. 115, no. 4, article 497, 1979.

[32] M. Grossin and S. Belaich, “Another case of focal acantholytic dyskeratosis in the anal canal,” *American Journal of Dermatopathology*, vol. 15, no. 2, pp. 194–195, 1993.

[33] M. Vazquez Botet and J. L. Sanchez, “Vesiculation of focal acantholytic dyskeratosis in acral lentiginous malignant melanoma,” *Journal of Dermatologic Surgery and Oncology*, vol. 5, no. 10, pp. 798–800, 1979.

[34] Y. E. Sanchez, E. Martin-Dorado, E. Lopez-Negrette et al., “Incidental epidermolytic hyperkeratosis (IEH): an epidemiologic study,” *American Journal of Dermatopathology*, vol. 22, article 352, 2000.

[35] E. Sanchez Yus, L. Requena, P. Simon, and C. Martin de Hijas, “Incidental acantholysis,” *Journal of Cutaneous Pathology*, vol. 20, no. 5, pp. 418–423, 1993.