Case #5

Acantholytic dyskeratotic epidermal nevus with histologic features of Darier's disease in a puppy

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A 2.7 kg, mixed-breed bitch presented at 8 months of age with a plaque on the right ventral hemithorax and a chain of papules along the ipsilateral limb from the truncal lesion to eroded nodules and keratoses on the paw. The owner reported that lesions were present when the dog was obtained at the age of 6 weeks. The keratoses had been debulked, but soon recurred.

The clinical diagnosis was epidermal nevus. Lesions on the thorax and leg were excised with margins using an electro-surgical unit; the keratosis on the paw was debulked; all tissues were submitted in formalin for histologic examination.

Suprabasilar acantholysis and dyskeratosis were the unique histologic features. Acantholysis in epidermis and follicular epithelium resulted in suprabasilar clefts. Dyskeratotic cells were numerous throughout the stratum spinosum and were rounded with intense cytoplasmic eosinophilia; nuclei were sometimes shrunken and basophilic, but frequently were hypochromic with a prominent nucleolus and perinuclear pallor. Neutrophil infiltration was limited to eroded areas. Basal keratinocytes were hyperplastic but well differentiated. Intact epidermis was acanthotic and hypergranulotic with compact orthokeratosis. Crusts of dyskeratotic acantholytic cells, degenerated leukocytes, keratin, and debris covered erosions.

Pemphigus vulgaris was ruled out because it is never linear clinically and acantholysis is generally limited to the first layer of the stratum spinosum and not associated with prominent dyskeratosis. Acantholytic dyskeratosis with suprabasilar clefting is the hallmark of Darier's disease (keratosis follicularis), a human syndrome caused by autosomal dominant mutation of *ATP2A2*, which encodes sarco-/endoplasmic reticulum Ca^{++}-ATPase isoform 2 (SERCA2). Lesions usually appear in the first or second decades of life and tend to be generalized and progressive. Grover's disease resembles Darier's disease histologically, but tends to be transient, to appear later, and is not associated with *ATP2A2* mutation. Hailey-Hailey disease (benign familial pemphigus) results from autosomal dominant mutation in *ATP2C1*. Benign familial pemphigus in dogs results in suprabasilar acantholysis mainly in skin over pressure points, ventral chest, and pinna. Dyskeratosis is not prominent.

Acantholytic dyskeratosis is noted in a variety of other cutaneous disorders, including canine erythema multiforme, and may be found focally as an incidental lesion. Viral papilloma was considered because of the dog's age and multiplicity of lesions, but immunohistochemistry for papillomavirus using a genus-specific polyclonal antibody was negative. Squamous cell carcinoma was eliminated from the differential diagnosis because neither atypia nor invasiveness was evident. Warty dyskeratoma and acantholytic acanthoma are usually solitary lesions in old people. Acantholytic actinic keratosis was ruled out because the lesion was probably congenital. An acantholytic dyskeratotic variant of linear epidermal nevus is recognized as a rare congenital or childhood lesion that may be unilateral and distributed along Blaschko's lines (dermatomes). Though localized Darier's disease with unilateral lesions and dermatomal distribution has been described (and attributed to mosaic mutation), we consider epidermal nevus the more appropriate diagnosis in our dog because lesions were congenital, nonprogressive, and unassociated with other manifestations of Darier's disease; furthermore, histologic features were different from those in other recognized dyskeratotic/acantholytic diseases.

The dog returned 3 months after biopsy for CO_2 laser vaporization of remaining abnormal tissue on the footpads. Therapy with a third-generation topical retinoid (adapalene; Differin^R) was instituted twice weekly at the time of bandage changes. Bandages were discontinued after 3 weeks and the owner applies adapalene daily to affected tissue. Although the footpads have not healed completely, no recurrence or development of additional lesions has been noted in the 7 weeks since treatment began and the dog bears weight on the affected leg for the first time.