Reticular Hyperpigmentation With Keratotic Papules in the Axillae and Groin

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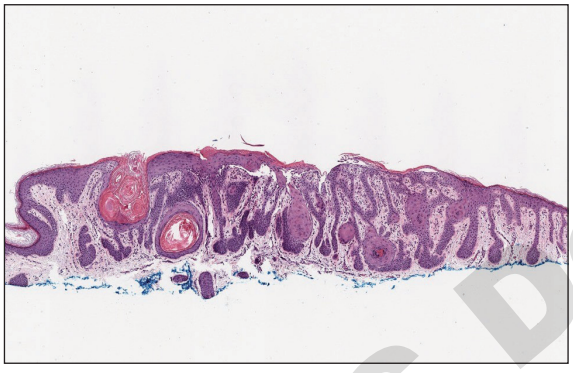

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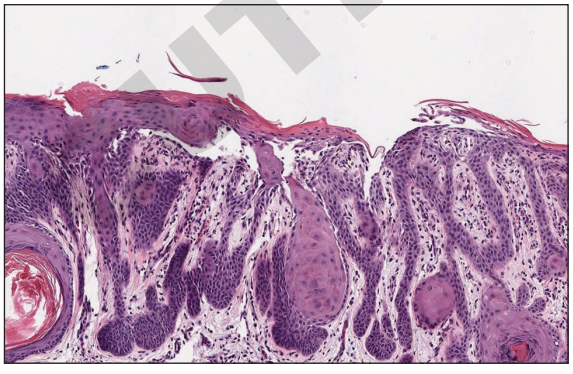

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A 37-year-old woman presented with multiple hyperkeratotic small papules in the axillae and groin of 1 year's duration. She reported pruritus and occasional sleep disruption. Subtle background reticulated hyperpigmentation was present. The patient reported that she had a great uncle with similar findings.

THE BEST **DIAGNOSIS IS:**

a. confluent and reticulated papillomatosis
b. Darier disease
c. Galli-Galli disease
d. Hailey-Hailey disease
e. pemphigus vulgaris

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THE **DIAGNOSIS:** Galli-Galli Disease

Several cutaneous conditions can present as reticulated hyperpigmentation or keratotic papules. Although genetic testing can help identify some of these dermatoses, biopsy typically is sufficient for diagnosis, and genetic testing can be considered for more clinically challenging cases. In our case, the clinical evidence and histopathologic findings were diagnostic of Galli-Galli disease (GGD), an autosomal-dominant genodermatosis with incomplete penetrance. Our patient was unaware of any family members with a diagnosis of GGD; however, she reported a great uncle with similar clinical findings.

Galli-Galli disease is a rare allelic variant of Dowling-Degos disease (DDD), both caused by a loss-of-function mutation in the keratin 5 gene, *KRT5*. Both conditions present as reticulated papules distributed symmetrically in the flexural regions, most commonly the axillae and groin, but also as comedolike papules, typically in patients aged 30 to 50 years.[1] Cutaneous lesions primarily are of cosmetic concern but can be extremely pruritic, especially for patients with GGD. Gene mutations in protein O-fucosyltransferase 1, *POFUT1*; protein O-glucosyltransferase 1, *POGLUT1*; and presenilin enhancer 2, *PSENEN*, also have been discovered in cases of DDD and GGD.[2,3]

Galli-Galli disease and DDD are distinguishable by their histologic appearance. Both diseases show elongated fingerlike rete ridges and a thin suprapapillary epidermis. The basal projections often are described as bulbous or resembling antler horns.[4] Galli-Galli disease can be differentiated from DDD by focal suprabasal acantholysis with minimal dyskeratosis (quiz images).[5] Due to the genetic and clinical similarities, many consider GGD an acantholytic variant of DDD rather than its own entity. Indeed, some patients have shown acantholysis in one area of biopsy but not others.[6]

Hailey-Hailey disease (HHD)(also known as benign familial or benign chronic pemphigus) is an autosomal-dominant disorder caused by mutation of the ATPase secretory pathway $Ca2^{+}$ transporting 1 gene, *ATP2C1*. Clinically, patients tend to present at a wide age range with fragile flaccid vesicles that commonly develop on the neck, axillae, and groin. Histologically, the epidermis is acanthotic with a dilapidated brick wall–like appearance from a few persistent intercellular connections amid widespread acantholysis (Figure 1).[7] Unlike in autoimmune pemphigus, direct immunofluorescence is negative, and acantholysis spares the adnexal structures. Hailey-Hailey disease does not involve reticulated hyperpigmentation or the elongated bulbous rete seen in GGD.

Confluent and reticulated papillomatosis is a rare, typically asymptomatic, hyperpigmented dermatosis. It presents as a conglomeration of scaly hyperpigmented macules or papillomatous papules that coalesce centrally and are reticulated toward the periphery. Confluent and reticulated papillomatosis most commonly is seen on the trunk, initially presenting in adolescents and young adults. Confluent and reticulated papillomatosis is histologically similar to acanthosis nigricans. Histopathology will show hyperkeratosis, papillomatosis, and minimal to no inflammatory infiltrate, with no elongated rete ridges or acantholysis (Figure 2).[8]

Pemphigus vulgaris is a blistering disease resulting from the development of autoantibodies against desmogleins 1 and 3. Similar to GGD, there is suprabasal acantholysis, which often results in a tombstonelike appearance consisting of separation between the basal

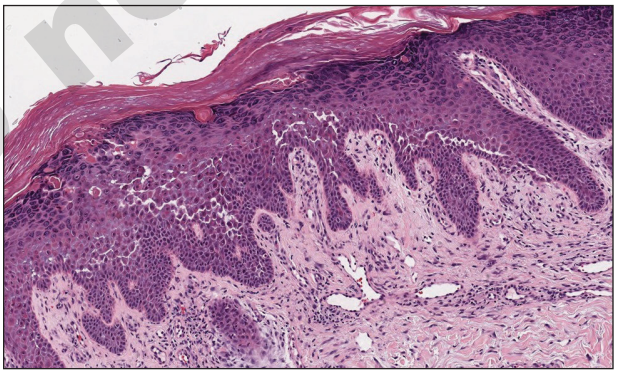

FIGURE 1. Hailey-Hailey disease. An acanthotic epidermis with suprabasal and intraepidermal acantholysis of keratinocytes resembling a dilapidated brick wall (H&E, original magnification ×100).

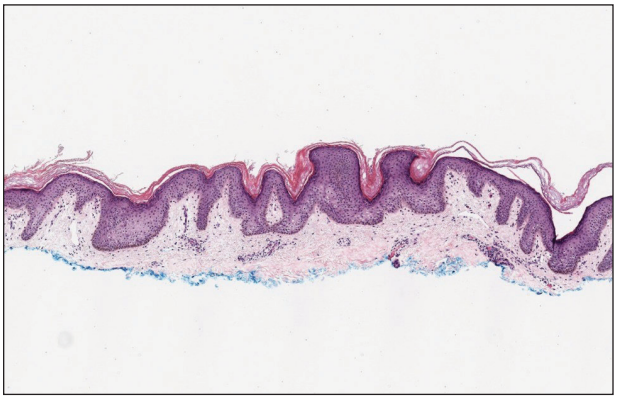

FIGURE 2. Confluent and reticulated papillomatosis. Hyperkeratosis, papillomatosis, and a sparse perivascular lymphocytic infiltrate (H&E, original magnification ×40).

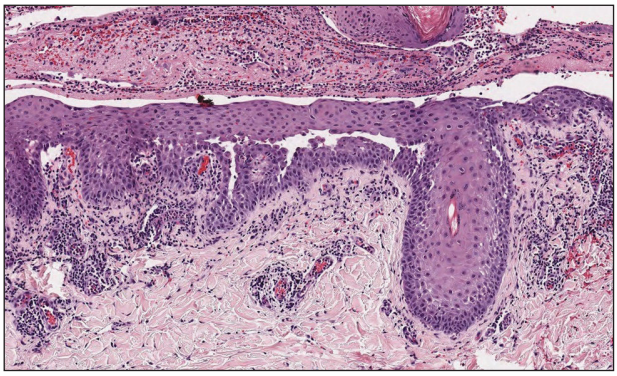

FIGURE 3. Pemphigus vulgaris. Acantholysis of the lower stratum spinosum and the hair follicle forming an intraepidermal blister (H&E, original magnification ×100).

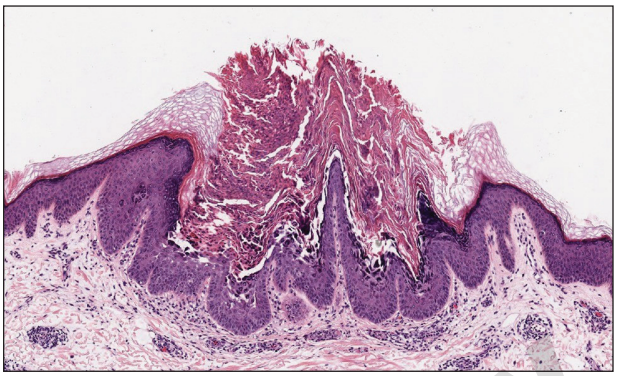

FIGURE 4. Darier disease. Parakeratotic hyperkeratosis and acantholytic dyskeratosis with corps ronds and grains (H&E, original magnification ×100).

layer cells of the epidermis but with maintained attachment to the underlying basement membrane zone. Unlike HHD, the acantholysis tends to involve the follicular epithelium in pemphigus vulgaris (Figure 3). Clinically, the blisters are positive for Nikolsky sign and can be both cutaneous or mucosal, commonly arising initially in the mouth during the fourth or fifth decades of life. Ruptured blisters can result in painful and hemorrhagic erosions.[9] Direct immunofluorescence exhibits a classic chicken wire–like deposition of IgG and C3 between keratinocytes of the epidermis. Although sometimes difficult to appreciate, the deposition can be more prominent in the lower epidermis, in contrast to pemphigus foliaceus, which can have more prominent deposition in the upper epidermis.

Darier disease (or dyskeratosis follicularis) is an autosomal-dominant genodermatosis caused by mutation of the ATPase sarcoplasmic/endoplasmic reticulum $Ca2^{+}$ transporting 2 gene, *ATP2A2*. Clinically, this disorder arises in adolescents as red-brown, greasy, crusted papules in seborrheic areas that may coalesce into papillomatous clusters. Palmar punctate keratoses and pits also are common. Histologically, Darier disease can appear similar to GGD, as both can show acantholysis and dyskeratosis. Darier disease will tend to show more prominent dyskeratosis with corps ronds and grains, as well as thicker villilike projections of keratinocytes into the papillary dermis, in contrast to the thinner, fingerlike or bulbous projections that hang down from the epidermis in GGD (Figure 4).[10]

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