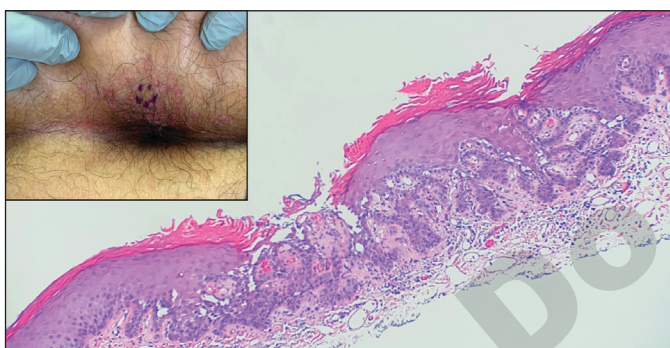


Pruritic Papules in the Perianal and Gluteal Cleft Regions

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H&E, original magnification $\times 20$.

A 66-year-old man presented to the dermatology clinic with pruritus of the gluteal cleft and perianal region of several months' duration. He had been prescribed permethrin by an outside physician, as well as oral acyclovir, triamcinolone-nystatin combination ointment, and topical zinc oxide prescribed by dermatology, without improvement. Physical examination showed several papules and erosions (<1 mm) in the perianal and gluteal cleft regions (inset). Hyperpigmented macules also were noted in the inguinal folds. A shave biopsy of a lesion from the perianal region was performed.

THE BEST DIAGNOSIS IS:

- Darier disease
- Grover disease
- Hailey-Hailey disease
- papular acantholytic dyskeratosis
- pemphigus vulgaris

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The authors report no conflict of interest.

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THE DIAGNOSIS: Papular Acantholytic Dyskeratosis

The shave biopsy revealed suprabasal clefts associated with acantholytic and dyskeratotic cells as well as overlying hyperkeratosis. Direct immunofluorescence (DIF) was negative. Based on the combined clinical and histological findings, the patient was diagnosed with papular acantholytic dyskeratosis (PAD), a rare disease that clinically presents as small whitish-greyish papules with the potential to coalesce into larger plaques.^{1,2} The condition predominantly manifests without symptoms, though pruritus and burning have been reported in affected sites. Most cases of PAD have been reported in older adults rather than in children or adolescents; it is more prevalent in women than in men. Lesions generally are localized to the penis, vulva, scrotum, inguinal folds, and perianal region.³ More specific terms have been used to describe this presentation such as *papular acantholytic dyskeratosis of the anogenital region* and *papular acantholytic dyskeratosis of the genital-crural region*. Histologic findings of PAD include epidermal acantholysis and dyskeratosis with hyperkeratosis and parakeratosis (quiz image).

The histologic differential diagnosis of PAD is broad due to its overlapping features with other diseases such as pemphigus vulgaris, Hailey-Hailey disease (HHD), Darier disease, and Grover disease. The acantholytic pathophysiology of these conditions involves dysfunction in cell adhesion markers. The correct diagnosis can be made by considering both the clinical location of involvement and histopathologic clues.

Pemphigus is a family of disorders involving mucocutaneous blistering of an autoimmune nature (Figure 1). Pemphigus vulgaris is the most prevalent variant of the pemphigus family, with symptomatically painful involvement of mucosal and cutaneous tissue. Autoantibodies to desmoglein 3 alone or both desmoglein 1 and 3 are present. Pemphigus vulgaris displays positive DIF findings with intercellular IgG and C3.

Hailey-Hailey disease (also known as benign familial pemphigus) is an autosomal-dominant disease that shares the acantholytic feature that is common in this class of diseases and caused by a defect in cell-cell adhesion as well as a loss of function in the ATPase secretory pathway Ca^{2+} transporting 1 gene, *ATP2C1*. Blistering lesions typically appear in the neck, axillary, inguinal, or genital regions, and they can develop into crusted, exudate-filled lesions. No autoimmunity has been associated with this disease, unlike other diseases in the pemphigus family, and mutations in the *ATP2C1* gene have been linked with dysregulation of cell-cell adhesion, particularly in cadherins and calcium-dependent cell adhesion processes. Histologically, HHD will show

diffuse keratinocyte acantholysis with suprabasal clefting (Figure 2).⁴ Dyskeratosis is mild, if present at all, and dyskeratotic keratinocytes show a well-defined nucleus with cytoplasmic preservation. In contrast to HHD, PAD typically shows more dyskeratosis.

Darier disease (also known as keratosis follicularis) is an autosomal-dominant condition that normally presents with seborrheic eruptions in intertriginous areas, usually with onset during adolescence. Darier disease is caused by a loss-of-function mutation in the *ATP2A2* gene found on chromosome 12q23-24.1 that encodes for the sarco(endoplasmic reticulum calcium ATPase2 (SERCA2) enzymes involved in calcium-dependent transport of the endoplasmic reticulum within the cell. Due to calcium dysregulation, desmosomes are unable to carry out their function in cell-cell adhesion, resulting in keratinocyte acantholysis. Histopathology of Darier disease is identical to HHD but displays more dyskeratosis than HHD (Figure 3), possibly due to the endoplasmic reticulum calcium stores that are affected in Darier disease compared to the Golgi apparatus calcium stores that are implicated in HHD.⁵ The lowered endoplasmic reticulum calcium stores in Darier-White disease are associated with more pronounced dyskeratosis, which is seen histologically as corps ronds. Suprabasal hyperkeratosis also is found in Darier disease. The histopathologic findings of Darier disease and PAD can be identical, but the clinical presentations are distinct, with Darier disease typically manifesting as seborrheic eruptions appearing in adolescence and PAD presenting as small white papules in the anogenital or crural regions.

Grover disease (also referred to as transient acantholytic dermatosis) has an idiopathic pathophysiology. It clinically manifests with eruptions of erythematous, pruritic, truncal papules on the chest or back. Grover disease has a predilection for White men older than 50 years, and symptoms may be exacerbated in heat and diaphoretic conditions. Histologically, Grover disease may show

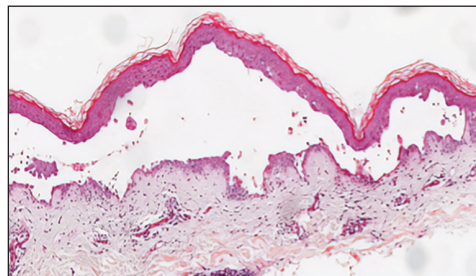


FIGURE 1. Pemphigus vulgaris. Intraepidermal blister demonstrating acantholysis and a suprabasal split (H&E, original magnification $\times 40$).

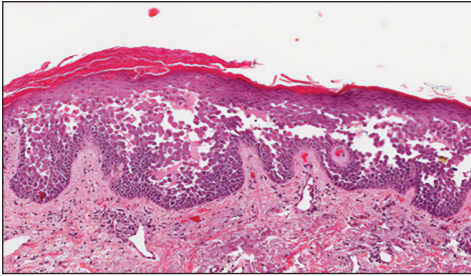


FIGURE 2. Hailey-Hailey disease. Intraepidermal acantholysis present at the spinous layer (H&E, original magnification $\times 40$).

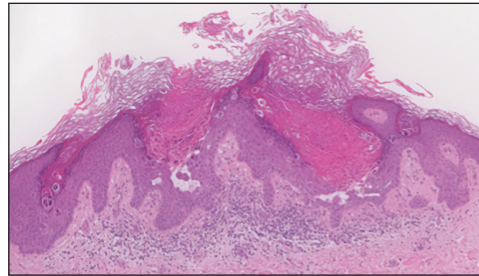


FIGURE 4. Grover disease. Focal acantholytic dyskeratosis with superficial predominantly lymphohistiocytic inflammation (H&E, original magnification $\times 40$).

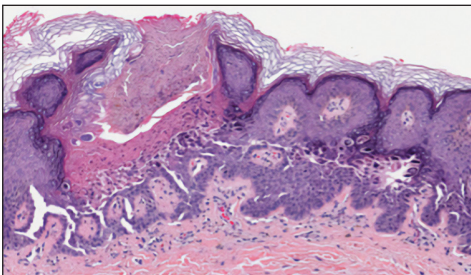


FIGURE 3. Darier disease. Acantholytic dyskeratosis with corps ronds and grains (H&E, original magnification $\times 40$).

acantholytic features seen in pemphigus vulgaris, HHD, and Darier disease; the pattern can only follow a specific disease or consist of a combination of all disease features (Figure 4). The acantholytic pattern of Grover disease was found to be similar to pemphigus vulgaris, Darier disease, pemphigus foliaceus, and HHD 47%, 18%, 9%, and 8% of the time, respectively. In 9% of cases, Grover disease will exhibit a mixed histopathology in which its acantholytic pattern will consist of a combination of features seen in the pemphigus family of diseases.⁶ Biopsy results showing mixed histologic patterns or a combination of different acantholytic features are suggestive of Grover disease over PAD. Moreover, the clinical distribution helps to differentiate Grover disease from PAD.

Because the histologic characteristics of these diseases overlap, certain nuances in clinical correlations and histology allow for distinction. In our patient, the diagnosis was most consistent with PAD based on the clinical manifestation of the disease and the biopsy results. Considering solely the clinical location of the lesions, Grover disease was a less likely diagnosis because our patient's lesions were observed in the perianal region, not the truncal region as typically seen in Grover disease.

Taking into account the DIF assay results in our patient, the pemphigus family of diseases also moved lower on the differential diagnosis. Finally, because the biopsy showed more dyskeratosis than would be present in HHD and also was inconsistent with the location and onset that would be expected to be seen in Darier disease, PAD was the most probable diagnosis. Interestingly, studies have shown mosaic mutations in *ATP2A2* and *ATP2C1* as possible causes of PAD, suggesting that this may be an allelic variant of Darier disease and HHD.⁷⁻⁹ No genetic testing was performed in our patient.

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