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Papular acantholytic dyskeratosis of the genitocrural area with positive direct immunofluorescence in a man affected by lichen sclerosus et atrophicus: a clinicopathological challenge

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Consent for publication: the patient gave his written consent to use his personal data for the publication of this case report and any accompanying images.

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Dear Editor,

Papular acantholytic dyskeratosis (PAD) is a rare, sporadic, persistent disease of adulthood, localized to the genitocrural and anogenital regions.[1] It was proposed as a new entity by Chorzelski *et al.* in 1984, based on the case of a 23-year-old woman with multiple, dome-shaped, white papules grouped on her vulva, which revealed histopathologically an epidermal proliferation with acantholysis and dyskeratosis, resembling both Haley-Haley (HHD) and Darier diseases (DD).[1] Since then, PAD was reported as an asymptomatic/slightly itchy eruption of multiple white to skin-colored papules, coalescing to plaques, more commonly around the vulva.[2-3] Cases among males were fewer.[4-5]

Despite its histopathological similarities to HHD and DD, PAD is considered a distinct entity, as it tends to be confined to the genitocrural region, the involvement of folds and seborrheic areas is absent, and no family history of similar eruptions is reported in these patients, helping clinicians to rule out HHD and DD, which are both autosomal dominant dermatoses. Although its etiopathogenesis is still unclear, recent evidence suggests that PAD can sometimes be associated with genetic mutations in *ATP2C1* (related to HHD)[6-7] and *ATP2A2* (related to DD).[8] Therefore, it was proposed that PAD could be a localized or mosaic form of these genetic acantholytic dermatoses.

PAD may represent a challenging diagnosis, both from a clinical and a histopathological point of view, as in a case that we encountered in our clinical practice. A 68-year-old man, in follow-up for a previous diagnosis of genital lichen sclerosus et atrophicus (LSA), referred to our Institution for a recently onset genital erosion resistant to topical treatments. The dermatological examination revealed an erosive and slightly hyperkeratotic plaque measuring 15×8 mm, located just next to the urethral meatus, in the context of a whitish and sclerotic appearance of the penis (Figure 1). There were no other lesions on intertriginous areas. Familiar history of similar eruptions was excluded, and serology for sexually transmitted infectious diseases, HPV test, and direct microscopic examination for fungi were negative. In the suspicion of a squamous cell carcinoma arising on LSA, two punch biopsies were performed. Microscopically, the one from the whitish sclerotic area surrounding the erosion confirmed the classical histopathological features of LSA, such as intense papillary edema, producing a dermolytic subepidermal bulla, and homogeneous sclerotic collagen with patchy lymphocytic infiltrates in the upper reticular dermis (Figure 2A). The specimen from the erosion showed epidermal hyperplasia with suprabasal clefting and “dilapidated brick wall” acantholysis, which was indistinguishable from HHD (Figure 2B). Part of this specimen was submitted for direct immunofluorescence (DIF), which revealed intraepidermal intercellular C3 and IgG deposition with a “net-like” pattern (Figure 2C). Further examination of specific anti-skin autoantibodies, particularly anti-desmoglein (Dsg) 1 and anti-Dsg3 antibodies, was negative, as it was also indirect

immunofluorescence. A diagnosis of PAD arising in the context of LSA was proposed for this case. As far as we are aware, the combination of these pathological entities has never been described in the male genital area.

This case poses a diagnostic challenge due to its peculiar clinicopathological features. It does not perfectly fit any previous report, as the characteristic presentation of multiple papules is lacking. Moreover, the association between PAD and LSA in the male genital area has not been previously documented. Haddadeen *et al.* published a case of vulvar PAD associated with genital LSA where the classical presentation of multiple papules was not found,[9] as in our case. These two reports may suggest a possible relationship between focal acantholytic dyskeratosis of the genital area and LSA.

Noteworthily, our patient showed positive DIF with a "net-like" pattern, without any family history of oral or cutaneous lesions, suggesting a possible pemphigus vulgaris. In the literature, rare cases of PAD have shown positive DIF, with intercellular C3 and IgG positivity in the epidermis.[10-11] These results may lead to misdiagnosis of these cases as pemphigus vegetans (especially the Hallopeau-type), a variant of pemphigus vulgaris characterized by flaccid blisters that become erosions and form papillomatous plaques with crusts in intertriginous areas. From a histopathological perspective, a diagnostic clue to this entity is intraepidermal eosinophilic abscesses, which were absent in our case. Furthermore, the presence of dyskeratosis associated with prominent suprabasal intraepidermal acantholysis, with a "dilapidated brick wall" appearance, and the absence of prominent inflammation excluded the diagnosis of pemphigus in our case.

No standardized treatment approach is approved for the management of PAD. As it is a benign disease, the protocol in asymptomatic patients is controversial, and long-term follow-up is generally the choice, as spontaneous regression was reported. On the other hand, whether symptoms are present, topical and systemic corticosteroids are the first-line therapy, but retinoids may also be effective.[12-13] Surgical excision and ablative laser therapy have been employed in cases not responding to medical approaches.[14] Recently, topical treatment with diclofenac sodium 3% gel was well-tolerated by the patient and led to complete remission of the disease.[15]

In conclusion, PAD may also occur with a peculiar clinical presentation of a single erosive plaque, especially in the context of genital LSA. DIF may be positive, but the autoimmunity profile is not supportive of pemphigus. The diagnosis of canonical PAD is already challenging for pathologists who are not aware of this entity. This case, with its unusual clinicopathological features, emphasizes the importance of recognizing this disease to reduce the risk of misdiagnosis.

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Figure 1. Clinical aspects. (**A**) Whitish discoloration and sclerotic appearance of the penis, associated with (**B**) an erosive and slightly hyperkeratotic lesion of the glans.

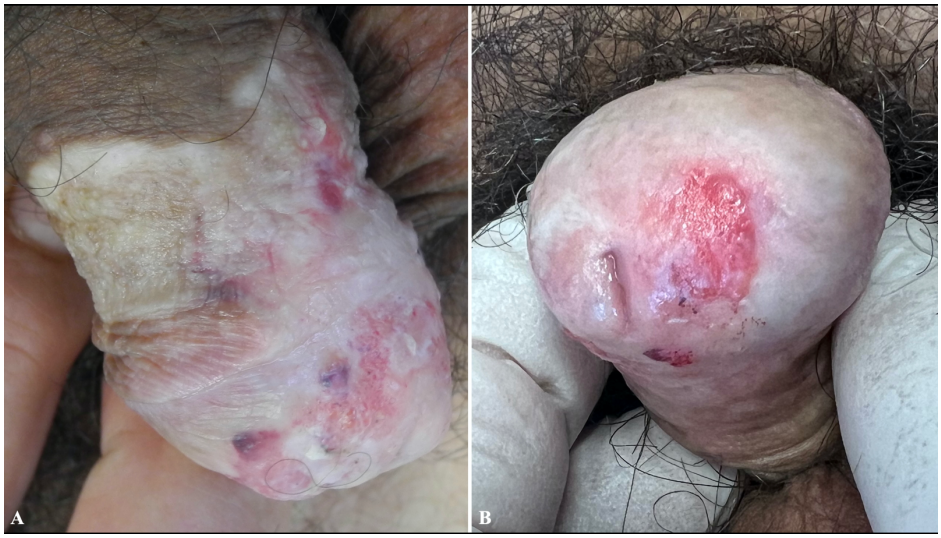

Figure 2. Histopathological and direct immunofluorescence aspects. (**A**) Intense papillary edema, producing a subepidermal bulla, and homogeneous sclerotic collagen with patchy lymphocytic infiltration. (**B**) Epidermal hyperplasia with suprabasal clefting and "dilapidated brick wall" acantholysis. In the inset, the panoramic view of the same biopsy specimen. (**C**) Intraepidermal intercellular IgG deposition with a "net-like" pattern.