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Multiple acantholytic dyskeratotic acanthomas in a liver-transplant recipient

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Abstract

Acantholytic dyskeratotic acanthoma is a rare variant of epidermal acanthoma characterized pathologically by the presence of acantholysis and dyskeratosis. Few cases have been reported until now, one of them in a heart-transplant patient. We present here a new case of this rare lesion that developed in a liver-transplant patient and review the salient features of this uncommon condition.

Keywords: acantholytic dyskeratotic acanthoma, acantholysis, dyskeratosis, immunosuppression, organ transplantation

Introduction

Acantholytic dyskeratotic acanthoma (ADA) is a rare variant of epidermal acanthoma, characterized microscopically by acantholysis and dyskeratosis. It was first reported as a distinct entity in 2007 [1] and an additional 35 cases have been reported since then [2-7], one of which was in a heart-transplant patient [6]. We report herein a new case of ADA diagnosed in a liver-transplant recipient and briefly review the salient clinicopathologic features of this entity and the differential diagnosis from pathologically similar lesions.

Case Synopsis

A 74-year-old man had received a liver allograft at the age of 61 years because of nodular regenerative hyperplasia related to HCV infection. His recent maintenance immunosuppressive treatment consisted of tacrolimus (1mg/d), everolimus (0.5mg/d) and prednisolone (5mg/d). He had recently developed end-stage renal disease and was undergoing hemodialysis. His post-transplant medical history was significant for two melanomas (one *in situ* on the abdomen diagnosed at the age of 61 years and a superficial spreading melanoma 2.4mm Breslow thickness of the dorsum of the foot diagnosed ten years later), a squamous cell carcinoma of the cheek, a basal cell carcinoma and actinic keratosis of the ear, and an atypical nevus of the chest. He was seen in September 2018 (at 74 years of age) for keratotic lesions of the back that had been noticed recently. Physical examination showed some red-brown keratotic, asymptomatic papules grouped on the lower back, admixed with seborrheic keratoses and melanocytic nevi (**Figure 1A**).

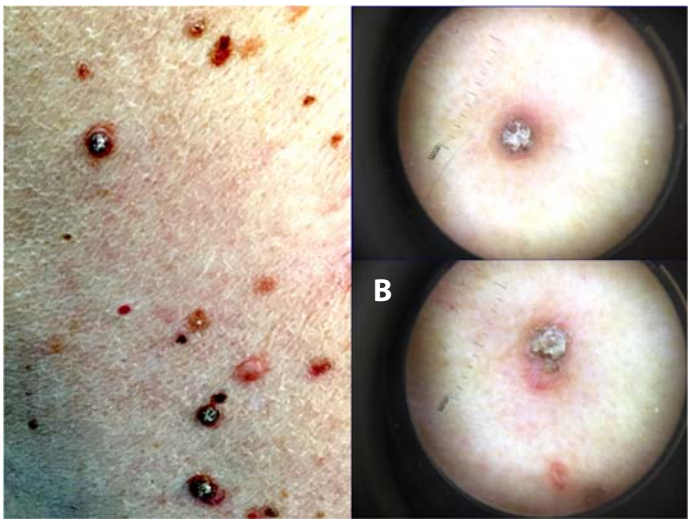

Figure 1. *Macroscopic appearance: red-brown keratotic papules clustered on the patient's back **A)**. Dermatoscopic examination shows red-brown papules devoid of pigment network, overlaid by grey hyperkeratosis **(B, C)**.*

Dermatoscopic examination of two lesions looking clinically similar showed the same findings, i.e. red-brown papules with no visible pigment network or vessels, overlaid by greyish hyperkeratosis (**Figures 1B, C)**. The patient had neither adnexal nor nail lesions and his family history was unremarkable for any similar skin conditions.

A representative lesion of the back was excised under local anesthesia. Microscopic examination (**Figure 2**) showed a well demarcated epidermal proliferative, cup-shaped lesion overlaid by a very thick horny layer containing within its lower layers dyskeratotic corneocytes ('grains'). The underlying epidermis showed moderate acanthosis and overall prominent papillomatosis, manifesting with thin basal cell layer epithelial downgrowths projecting into the papillary dermis. They contained acantholytic clefts, within which dyskeratotic and acantholytic keratinocytes were seen. The granular layer was thick and contained large, round dyskeratotic keratinocytes separated from the adjacent cells by clefts ('corps ronds'). No association with hair follicles was obvious. The upper dermis contained a moderately dense, mainly lymphocytic, infiltrate. On the basis of these clinicopathologic findings, the diagnosis of multiple acantholytic dyskeratotic acanthomas was made.

Case Discussion

Acantholytic dyskeratotic acanthoma (ADA) is a rarely reported variant of acanthoma associating microscopically the findings of acantholysis and dyskeratosis. It belongs to the spectrum of diseases showing acantholytic dyskeratosis, including namely Darier disease, Grover disease, warty dyskeratoma, familial dyskeratotic comedones, acantholytic dermatosis of the genitocrural area, and familial benign pemphigus/Hailey-Hailey disease. Till the present to our knowledge, 36 cases of ADA have been reported [1-7], including the present one. The mean age at diagnosis is 55 years (range 39-84) and a slight female predominance exists [4]. Clinically, ADA manifests usually as an asymptomatic single keratotic papule or plaque measuring on average 5mm, located predominantly (in two thirds of the cases) on the trunk or the extremities [4]. Remarkably, the two ADA cases reported in the transplant setting [6], and this case, manifested with multiple lesions. ADAs have no distinctive clinical features and have been most often diagnosed clinically as basal or squamous cell carcinoma, actinic keratosis, or seborrheic keratosis [4]. Clinically, they have some resemblance with reactive perforating collagenosis, a condition also associated with end-stage renal disease [8]. There is no family history, differentiating ADA from genodermatoses with acantholytic dyskeratosis (Darier's disease and Hailey-Hailey disease). Four cases of subungual ADA have been reported on the thumb, manifesting with longitudinal erythronychia or xanthonychia [3, 7].

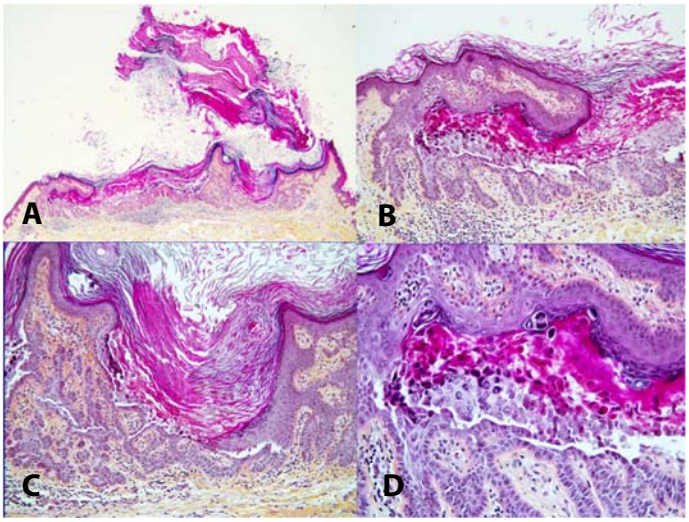

Figure 2. *Microscopic aspect: Low-power magnification shows an endo-exophytic, well-demarcated papule overlaid by massive hyperkeratosis **A)**. At higher magnification, papillomatosis of the epidermis, which contains acantholytic clefts, is seen **(B, C)**. Dyskeratotic keratinocytes ("corps ronds") are clearly seen **D)**. (H&E, **A**, 40×; **B**, **C**, 100×; **D**, 250×.).*

The diagnosis of ADA is made upon microscopic examination. The differential diagnosis of (multiple) ADA includes lesions comprising microscopically a combination of acantholysis and dyskeratosis, mainly Darier disease (DD), Grover disease, warty dyskeratoma, acantholytic dermatosis of the genitocrural area, familial dyskeratotic comedones, and familial benign pemphigus/Hailey-Hailey disease (HHD). Darier disease is an autosomal dominant genodermatosis owing to mutations of the *ATP2A2* gene; it manifests with widespread cutaneous (and nail) lesions, an onset early in life, and positive family history. Grover disease is an acquired condition manifesting with pruritic

erythematous papulovesicular lesions of the trunk, which are less keratotic; they are triggered by heat or UV-exposure and usually are transient, regressing within weeks or months. Hailey-Hailey disease, an autosomal-dominant genodermatosis owing to mutations of the *ATP2C1* gene, manifests with crusted and eroded plaques on intertriginous areas in a family setting. Microscopically, it shows more prominent acantholysis than dyskeratosis, with a characteristic aspect of the 'dilapidated brick wall.' Acantholytic dermatosis of the genitocrural area is an acquired condition affecting mainly young to middle-aged patients with no family history. This condition manifests with small, variable pruritic papules localized on the genitocrural area. Familial dyskeratotic comedones, a rare dermatosis manifesting with comedo-like keratotic papules predominating on the extremities, is an autosomal dominant familial condition. The lesion most closely resembling ADA is warty dyskeratoma. This manifests usually as a solitary, tumor-like papulonodular growth predominating on the head/neck area (contrary to ADA, which have been diagnosed in extracephalic sites); pathologically, it shows a deeply invaginating cup-shaped or cystic nodule, occasionally in association with hair follicles [9, 10], a feature not seen in ADA. Warty dyskeratoma may rarely manifest with multiple lesions, which in that case usually affect the scalp [11]. Acantholytic acanthoma is another variety of acanthoma displaying acantholysis but not dyskeratosis. Of note, acantholysis and/or dyskeratosis can be seen as an incidental finding in a variety of unrelated conditions lacking a specific clinical appearance [12, 13].

The pathogenesis of ADA is unknown. The pathological similarity of ADA with DD and HHD and the fact that one case of ADA developed under vemurafenib treatment [5], (known to induce acantholysis via an increased cytosolic calcium concentration), [14], suggest that imbalance of calcium metabolism within the cell could play a role. Of note, patients with ADA have no personal or family history of DD or HHD. However, no study has so far searched for mutations of the *ATP2A2* and *ATP2C1* genes, responsible for DD and HHD, respectively.

Conclusion

Organ transplant recipients are known to be at risk for developing various hyperplastic and neoplastic epidermal proliferations. Acantholytic acanthomas [15], epidermolytic acanthomas [16], Grover disease [17, 18] and Galli-Galli disease [19] have already been reported in this patient group; the latter two conditions also microscopically exhibit acantholysis and/or dyskeratosis. The case presented herein and the previously reported similar case [6] suggest that ADA should be added to the list of benign epidermal proliferations that may develop in the transplant setting. Contrary to the remaining cases, both these patients presented with multiple lesions, suggesting that immunosuppression may favor the development of multiple ADA.

Potential conflicts of interest

The authors declare no conflicts of interests.

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