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CASE REPORT

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Acquired epidermodysplasia verruciformis in renal-transplant recipients

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Abstract

Acquired epidermodysplasia verruciformis in renal-transplant recipients is associated with a high risk for developing squamous cell carcinoma. An accurate diagnosis and a regular monitoring in this high-risk population must be stressed.

KEYWORDS

dermatology, health maintenance, nephrology, oncology

1 | INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare autosomal recessive genodermatosis, associated with a high susceptibility to infection with particular genotypes of human papillomaviruses (HPV) that are innocuous for the general population. Acquired forms of EV have been recently distinguished as an entity occurring in immunocompromised patients such as HIV-infected subjects or organ-transplant recipients.[1] Clinical presentation can be variable, often similar to the inherited forms. Studies reporting acquired EV in renal-transplant recipients are scarce. Herein, we report a case of an acquired EV in a renal-transplant recipient and review the available literature data.

2 | CASE REPORT

A 30-year-old male patient with a four-year history of kidney transplantation for indeterminate nephropathy with end-stage renal disease and who was treated at our department for a drug reaction to amphotericin B he had received for a visceral leishmaniasis presented for a recurrence of the cutaneous eruption, evolving for the last 6 days. He was under post-transplant maintenance immunosuppressive therapy including prednisone, mycophenolate mofetil, and tacrolimus. Physical examination revealed multiple erythematous and confluent macules and papules of the torso and abdomen (Figure 1A-C). No verrucous lesions or tinea versicolor-like lesions were found. A skin biopsy of the macules was performed. Histological examination showed, in the upper epidermis, foci of keratinocytes of increased size, with enlarged nuclei and a bubbly, bluish, abundant cytoplasm, containing variably sized keratohyaline granules (Figure 2). There were no signs of drug reaction. Histological features were consistent with the diagnosis of acquired EV. There was no history of affected relatives. A regular sunscreen application and close follow-up were proposed.

3 | DISCUSSION

Epidermodysplasia verruciformis is a rare inherited genodermatosis characterized by an increased susceptibility to

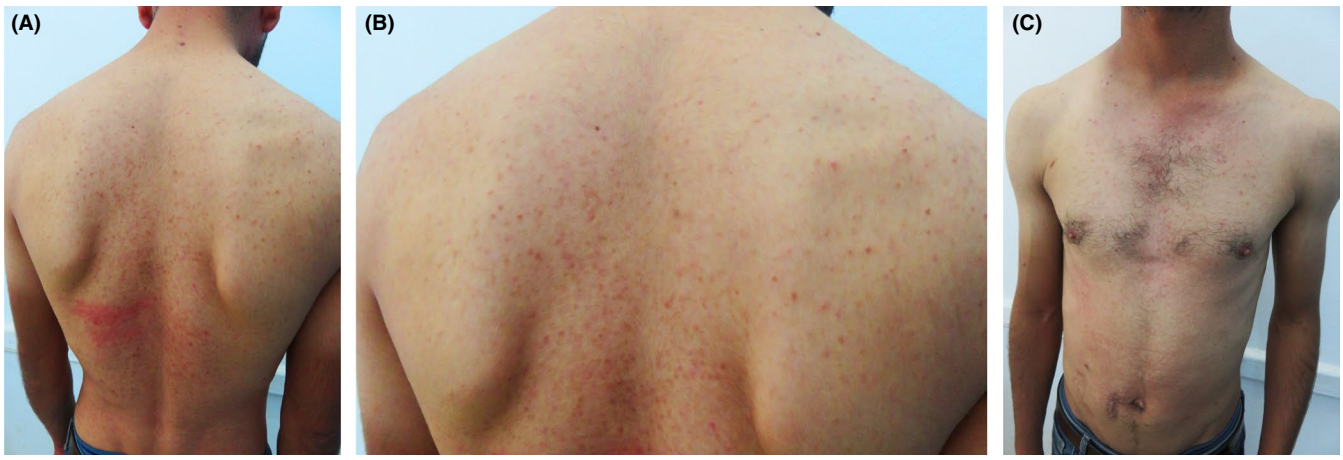

FIGURE 1 (A, B, C) erythematous papules of the trunk

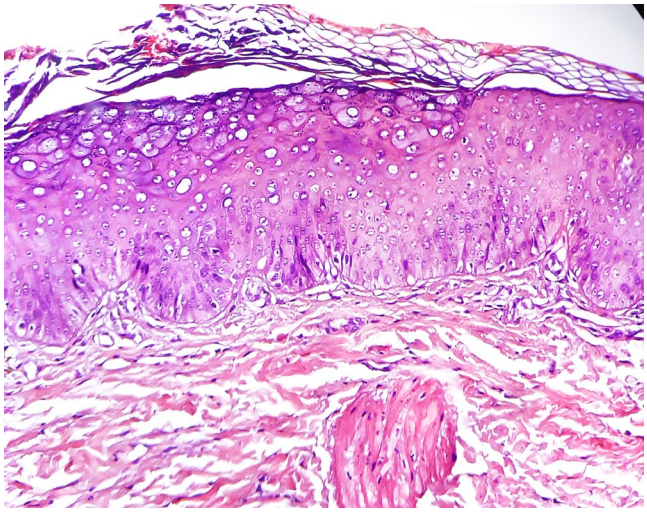

FIGURE 2 Skin biopsy specimen (hematoxylin-eosin stain; original magnification: ×40): in the upper epidermis, large keratinocytes with enlarged nuclei, a bubbly bluish cytoplasm and variably sized keratohyaline granules

specific genotypes of human papillomaviruses (HPV).[2] HPV 5 and HPV 8 are reported to be the major causative agents. Causal genetic mutations have been identified in the EVER genes.[3] The etiopathogenesis is multifactorial, involving viral, genetic, and environmental factors. Over time, affected subjects have an increased risk of squamous cell carcinoma on sun-exposed areas. In 1983, Lutzner and colleagues had detected, in a renal-allograft recipient, HPV 5 DNA, in both squamous cell carcinomas and benign skin lesions that resemble clinically and histologically to the lesions of inherited EV. They suggested a synergistic action between HPV infection, immunosuppression, and sunlight exposure in the occurrence of skin carcinoma in renal-transplant recipient.[4] Acquired EV is a term coined in 2009 by Rogers and colleagues to describe acquired phenotypes of EV discovered in HIV patients.[5] Other conditions of suppressed cellular immunity have been associated with acquired EV such as systemic lupus erythematosus,[6] GVH disease,[7] atopic dermatitis,[8] and solid organ transplantation such as renal transplantation.[9] The description of acquired EV in immunocompromised hosts suggests the potential role of a specific immune deficiency. A novel classification for the different types of EV subdivides the disease into genetic EV (classic and nonclassic according to the mutations) and acquired EV.[10] Although an underlying genetic susceptibility to HPV infection in immunocompromised patients with acquired EV has been hypothesized, it has not yet been identified.

Clinically, acquired EV manifests usually with the same features as genetic EV, namely a tinea versicolor-like eruption of the trunk, face, and extremities and verruca-like lesions on the distal extremities.[2] Published data about acquired EV related to renal transplantation are scarce with mainly single case reports. Table 1 shows all reported clinical cases of acquired EV in renal-transplant recipients. Most cases have a typical presentation.[9,11,12] In other papers, the presentation was atypical with lesions limited to the perineum[13] and the inguinal folds.[14] A case of acquired EV mimicking a periungual malignant melanoma was reported in a patient diagnosed with a cutaneous T-cell lymphoma.[15] In our case, tinea versicolor-like lesions and verrucous lesions were absent, and the diagnosis was made by a fortuitous biopsy for a drug reaction suspicion. HPV types associated with lesions in acquired EV are the same as those associated with genetic EV.[2] In our case, HPV genotyping has not been studied.

As for cancer susceptibility, the progression to nonmelanoma skin cancers in acquired EV has not been well documented.[2,5] In organ-transplant recipients, the use of immunosuppressive medications to prevent organ rejection is responsible for increasing the susceptibility for viral infections, particularly HPV, that may explain the occurrence of the acquired EV phenotypes. In his report, Mendes highlights the role of post-transplantation immunosuppressive medications in increasing both the susceptibility for viral infections and the rate of malignancies. This effect is caused by most of the

TABLE 1 Characteristics of cases of acquired epidermodysplasia verruciformis in renal-transplant recipients

Case reference	Sex	Age (y)	Underlying disease	Medications	Clinical aspects	Location	HPV type	Histology	Treatment
1 [Our case]	M	30	Glomerulonephritis	MMF, prednisone, azathioprine	Erythematous macules and papules	Torso, abdomen	-	In the epidermis, keratinocytes of increased size, with enlarged nuclei and a bubbly, bluish, cytoplasm that contains keratohyaline granules	-
2[9]	M	24	Systemic lupus erythematosus With lupus nephritis	MMF Prednisone sirolimus	Erythematous papules and macules	Face, neck, V-shaped neckline forearms, abdomen	-	Vacuolated cells in the upper epidermis, bubbly bluish cytoplasm, thickened granular layer, perivascular infiltrate in the superficial dermis	-
3[14]	F	50	Alport syndrome	Tacrolimus MMF prednisolone	Erythematous, flat-topped papules	Inguinal folds extending to the upper thighs	5	Enlarged keratinocytes with a blue-gray cytoplasm, vacuolated cells in the upper epidermis and coarse keratohyaline granules	Topical tretinoin 0.05% + topical imiquimod 5% +acitretin 10 mg daily + three Gardasil vaccinations
4[11]	F	44	Systemic lupus erythematosus	Cyclosporine, MMF, prednisone	Several grouped pink lichenoid macules	Upper mid-chest, anterior neck, left leg	-	Viral epidermal cytopathic changes, blue cytoplasm, coarse hypergranulosis	Cryosurgery, Tazarotene cream 0,05%, imiquimod cream5%, 5-fluorouracil cream 5%
5[13]	F	66	Hypertension	Prednisone MMF	Multiple papules coalescing into plaque	Perineum and perianal skin	5	Superficial keratinocytes with light gray cytoplasm surrounding slightly hyperchromatic and irregular nuclei	Curettage
6[12]	F	19	Glomerulonephritis	MMF tacrolimus prednisone	Erythematous papules	Trunk, upper limbs	23	Keratinocytes with vacuolated Cytoplasm	
7[4]	M	35	Glomerulonephritis	Azathioprine, prednisone	Macular, scaly lesions, resembling the pityriasis-versicolor-like lesions multiple in situ and invasive skin cancers in sun-exposed skin	Arms, trunk	5	-	

Abbreviation: MMF, mycophenolate mofetil.

molecules used.[9] In the cases of the literature, all renal-transplant recipients were undergoing maintenance immunosuppressive therapy.[7,9-14] These immunosuppressant molecules are known to increase the risk of malignancy.[16] Because of a similar pathophysiology to genetic EV, acquired EV may be associated with a higher rate of cutaneous cancers. The cumulative effect of these two risks in renal-transplant recipients is still unknown, and an intensification of the monitoring could be an option. As a precaution, photoprotection is mandatory.

No effective curative treatment has yet been discovered for neither the genetic nor the acquired forms.[2,5] Several treatment options have been proposed. However, no modality has been shown to be consistently successful. A case of an acquired EV in a renal-transplant recipient that cleared with a multimodal therapy including gardasil vaccination has been reported.[14]

4 | CONCLUSION

Acquired EV is a recent and rare entity, occurring in conditions with compromised cell-mediated immunity such as renal transplantation. The number of renal-transplant recipients has significantly increased in recent years which may lead to an increase in the prevalence of acquired EV. Transplant recipients are at high risk of developing nonmelanoma skin cancers.[16] It is important to recognize and accurately diagnose acquired EV because its impact on the cancer risk and its consequences on patient monitoring is still unknown. Cohort studies are required with long-term follow-up and continued evaluation to assess the relative risk for secondary skin cancers. The importance of regular sunscreen application must be stressed. Physicians should play a key role for the long-term dermatologic surveillance of this high-risk population.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Soumaya Gara, Meriem Jones, Noureddine Litaiem, Hafedh Hedri, Soumaya Rammeh and Faten Zeglaoui: participated in the management of this patient as well as in the preparation and edition of the manuscript. All authors read and approved the final manuscript.

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