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Acquired epidermodysplasia verruciformis in a renal transplant patient: a case report

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Abstract

Acquired epidermodysplasia verruciformis is a rare disease. It can develop in immunocompromised patients due to infection with human papillomaviruses. Because such patients are at high risk of developing cutaneous squamous cell carcinoma, timely diagnosis and regular monitoring of the patient is essential. Here we present the case of a 46-year-old male patient with acquired epidermodysplasia verruciformis occurring 5 years after a kidney transplantation. A skin biopsy detected human papillomavirus genotype 20 with low oncogenic potential. Accordingly, a follow-up interval of 1 year was determined. He was instructed to follow strict photoprotection and to visit earlier if atypical lesions appeared. Overall, our case emphasizes the consideration of possible squamous cell carcinoma in such patients and the importance of appropriate preventive measures.

Keywords: epidermodysplasia verruciformis, renal transplant, HPV 20, immunosuppression, imiquimod

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Introduction

Acquired epidermodysplasia verruciformis (AEV) is a rare dermatosis that has recently been recognized in patients with impaired cell-mediated immunity (1). AEV has been reported in patients with human immunodeficiency virus (HIV), non-Hodgkin lymphoma, systemic lupus erythematosus, graft versus host disease (GVHD), and atopic dermatitis treated with cyclosporine, and following solid organ transplantation (2). It is caused by human papillomavirus (HPV) infection. Importantly, it is believed that AEV may progress to cutaneous squamous cell carcinoma (SCC) with concomitant immunosuppression and HPV infection. However, because this is a recent observation, more data from larger studies and registries are still needed (1, 3).

Case report

A 46-year-old male patient was examined at the dermatology outpatient clinic due to erythematous, flat-topped papules on the skin of the upper part of trunk and both arms appearing 5 years after renal transplantation (Fig. 1). Due to renal transplantation, he was on systemic immunosuppressive therapy with methylprednisolone, mycophenolate mofetil, and tacrolimus. Based on clinical presentation, AEV was suspected, which was confirmed by histopathological examination. The skin lesions were first treated with cryotherapy, which resulted in flattening of the erythematous papules. Due to insufficient improvement, the patient was later treated with 5% imiquimod cream, five times weekly for 6 weeks. Because he was immunocompromised, a clinical reaction to treatment with imiquimod could not be predicted, and so we initially treated him with imiquimod only on the right part of the upper trunk. Interestingly, despite being immunocompromised, he developed a significant cutaneous reaction with pronounced itching and burning erythema. Therefore, in week 5 the treatment was discontinued. At the follow-up visit after 2 months, the lesions faded and became flat (Fig. 2). Before we continued the treatment, we obtained two skin biopsies for PCR detection of HPV genotypes: one from the region where the lesions were previously treated with imiquimod and the other from the area not treated yet. Two additional biopsies were performed because we wanted to know whether treatment with 5% imiquimod had eradicated HPV from the treated area and, second,

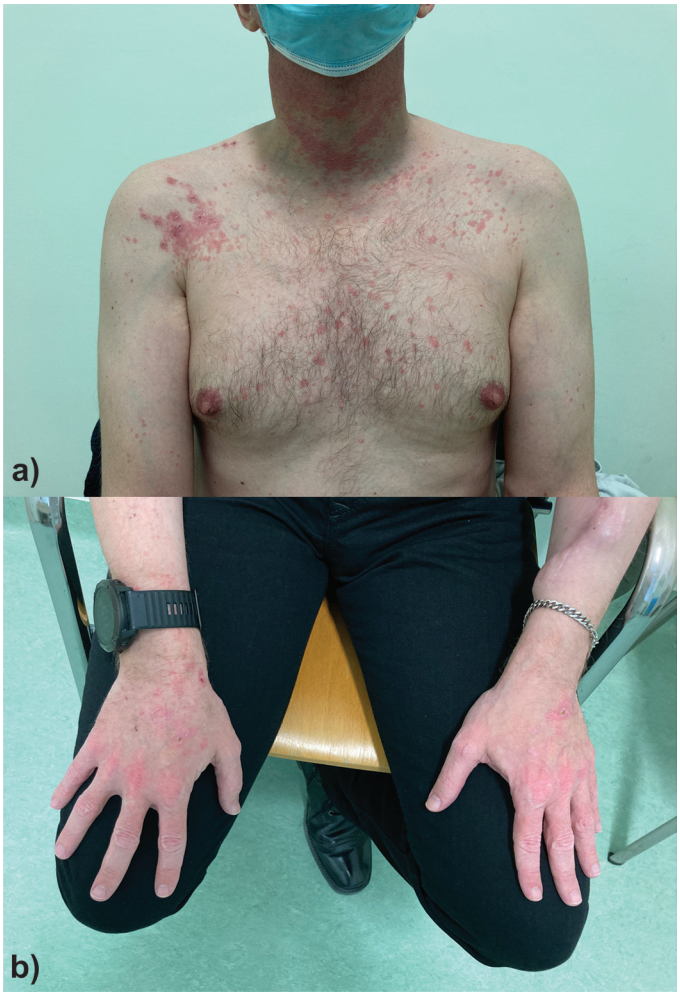

Figure 1 | Clinical presentation at the first visit: erythematous, flat-topped papules on the skin of the upper part of (a) the trunk and (b) both arms.

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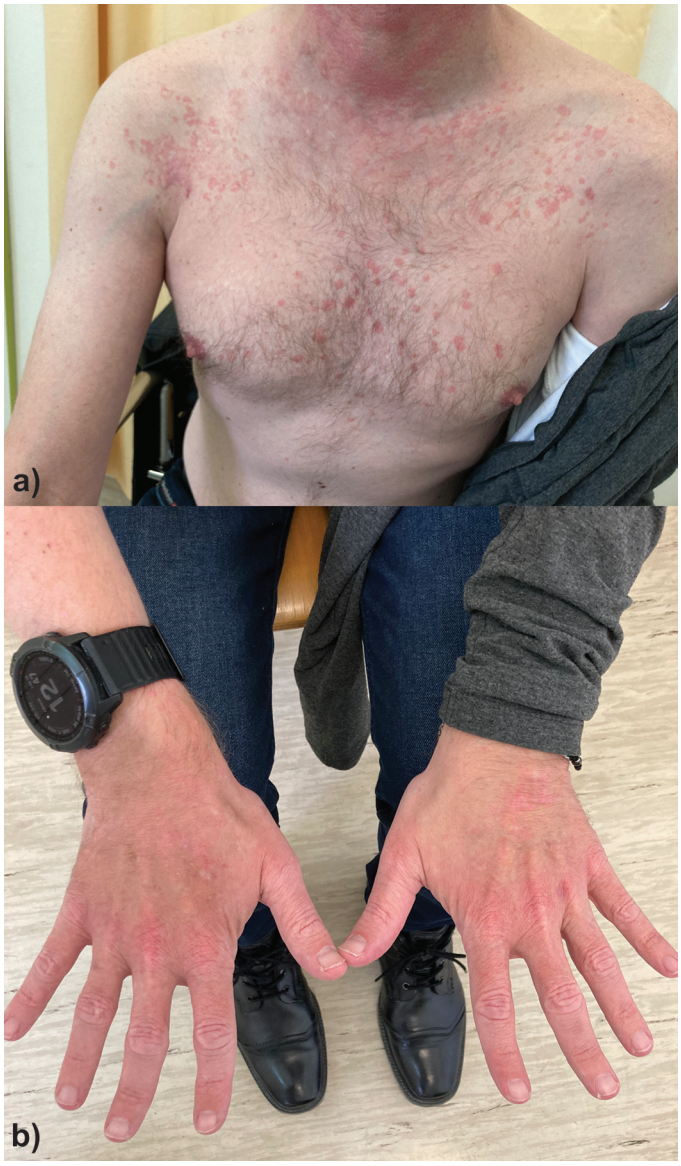

Figure 2 | Clinical presentation at the follow-up visit, after treatment with 5% imiquimod cream: light pink macules on (a) the upper trunk and (b) arms.

to estimate the oncogenic risk potential of present HPV. HPV genotype 20 was detected in both skin samples. At the follow-up, we also decided to treat the previously untreated lesions (left side) with imiquimod. Due to the marked cutaneous reaction after the first treatment regime (five times weekly for 6 weeks), we modified the treatment scheme to three times weekly for 4 weeks. However, no reaction was observed, and so we tried the first treatment regime, which yielded similar clinical results: the lesions faded and became flattened. Because HPV genotype 20 had been isolated, it was agreed that the patient would be monitored once a year. The patient was additionally instructed about strict photoprotection and was told to come earlier in the case of atypical lesions.

Discussion

EV is a rare inherited dermatosis characterized by chronic HPV infection. In addition to the inherited form of the disease, there is also an acquired form of EV, which typically occurs in patients with impaired cell-mediated immunity. It is known that the incidence of HPV-related conditions, such as condylomata accuminata or viral warts, is higher than in immunocompetent people (3). Although AEV is currently considered a rare disorder, it is assumed that, with extension of life expectancy of immunocompromised patients and the growing number of such patients, the incidence of AEV will also increase significantly in the future.

AEV typically presents as multiple pink to erythematous, pityriasis versicolor–like macules or flat-topped papules, rarely as verrucous or papillomatous lesions, distributed on sun-exposed skin, most commonly over the trunk, arms, and legs. Interestingly, lesions can exhibit the Koebner phenomenon (4). Treatment of AEV is usually unsatisfactory, despite many treatment modalities, including topical and systemic retinoids, cryotherapy, imiquimod, 5-fluorouracil, laser ablation, photodynamic therapy, and HPV vaccination (5–7).

When evaluating and managing immunocompromised patients with AEV, our main concern is possible progression to SCC (3). It is believed that chronic epidermal dysplasia in AEV carries the potential for evolution into SCC (8). The risk of progression is probably even higher when there is infection with HPV genotypes with higher oncogenic potential, such as genotypes 5, 17, and 47 (9, 10). This risk is further increased in the setting of long-term immunosuppression and in those frequently exposed to the sun (8). It is thought that HPV and ultraviolet (UV) light may act synergistically when this involves possible progression to SCC in AEV (11).

The most commonly isolated HPV genotypes in AEV are 5 and 8 (8, 12). In our patient, HPV 20 was isolated from both treated and untreated sites. HPV 20 is regarded as having low oncogenic potential. In our case, due to the strong reaction to imiquimod, eradication of HPV after treatment with immune response modifier cream was predicted. However, according to a study by Chen, eradication of HPV with imiquimod in genital intraepithelial neoplasia is only 60% (13). It can be speculated that with low-oncogenic HPV genotypes imiquimod could be even less effective at eradicating HPV, as was the case in our patient. In addition, imiquimod may have been less effective because our patient was immunocompromised.

In the case of iatrogenic immunosuppression, prednisolone, mycophenolate mofetil, and mTOR inhibitors (e.g., sirolimus and everolimus) exhibit anti-angiogenic effects with inhibition of UV-induced keratinocytic cancers (14). Therefore, if possible, those medications should be preferred instead of calcineurin inhibitors (tacrolimus or pimecrolimus) in patients with AEV to reduce the risk of possible progression to SCC (4, 14). Obviously, consultation with a nephrologist is needed in such cases. In our case, we consulted a nephrologist, who felt no need to change the treatment.

When treating patients with AEV, it is important to estimate the risk of possible progression of skin lesions into SCC, and therefore we determined the genotype of HPV involved. Because there are no recommended guidelines regarding a follow-up period based on the HPV genotype and consequent possible progression to SCC in AEV patients, in our patient we decided to follow up with him once a year. It is also important to bear in mind other risk factors for possible SCC development, such as frequent sun exposure.

Regarding AEV patients, there are several questions that remain unanswered, including effective treatment and more precise estimation of the risk of SCC, also based on the HPV genotype and the need for vaccination of immunocompromised patients. Because the life expectancy of immunosuppressed patients is growing, an increased incidence of AEV and new insights into this disease can be expected.

Conclusions

With this case report we would like to emphasize that, when treating immunocompromised patients with skin rashes, it is necessary to bear in mind a wide range of differential diagnoses, including AEV. Despite many treatment modalities, the treatment usually remains unsatisfactory. Our case emphasizes consideration of possible SCC in such patients and the importance of appropriate preventive measures. Evaluation of patients with AEV should consist of estimation of risk factors for progression of lesions into SCC, including the oncogenic potential of existing HPV genotype, sun exposure, duration of immunosuppression, and immunosuppressive medications. The role of the dermatologist is also to educate patients with AEV about possible preventive measures and regular self-assessment. New studies are needed to estimate the risk of SCC development in AEV patients. New insight into the disease would guide dermatologists in deciding on the right treatment option and determining the right follow-up period for every individual AEV patient.

References

1. Rogers HD, MacGregor JL, Nord KM, Tyring S, Rady P, Engler DE, et al. Acquired epidermodysplasia verruciformis. JAAD. 2009;60:315–20.
2. Gara S, Jones M, Litaiem N, Hedri H, Rammeh S, Zeglaoui F. Acquired epidermodysplasia verruciformis in renal-transplant recipients. Clin Case Rep. 2020;8: 2678–81.
3. Przybyszewska J, Zlotogorski A, Ramot Y. Re-evaluation of epidermodysplasia verruciformis: reconciling more than 90 years of debate. JAAD. 2017;76:1161–75.
4. Moore S, Rady P, Tyring S. Acquired epidermodysplasia verruciformis: clinical presentation and treatment update. Int J Dermatol. 2021. [Online ahead of print].
5. Zampetti A, Giurdanella F, Manco S, Linder D, Gnarra M, Guerriero G, et al. Acquired epidermodysplasia verruciformis: a comprehensive review and a proposal for treatment. Dermatol Surg. 2013;39:974–80.
6. Maor D, Brennand S, Goh MS, Fahey V, Tabrizi SN, Chong AH. A case of acquired epidermodysplasia verruciformis in a renal transplant recipient clearing with multimodal treatment including HPV (Gardasil) vaccination. Aust J Dermatol. 2018;59:147–8.
7. Henley JK, Hossler EW. Acquired epidermodysplasia verruciformis occurring in a renal transplant recipient. Cutis. 2017;99:E9–12.
8. Mendes AD, Bittencourt M de J, Moure ER, D'Macêdo CM, Yamaki IN, Araújo DM. Acquired epidermodysplasia verruciformis in a renal transplant recipient—case report. An Bras Dermatol. 2014;89:144–6.
9. Adachi A, Kiyono T, Hayashi Y, Ohashi M, Ishibashi M. Detection of human papillomavirus (HPV) type 47 DNA in malignant lesions from epidermodysplasia verruciformis by protocols for precise typing of related HPV DNAs. J Clin Microbiol. 1996;34:369–75.
10. Yutsudo M, Shimakaget T, Hakura A. Human papillomavirus type 17 DNA in skin carcinoma tissue of a patient with epidermodysplasia verruciformis. Virology. 1985;144:295–8.
11. Iannacone MR, Wang W, Stockwell HG, O'Rourke K, Giuliano AR, Sondak VK, et al. Sunlight exposure and cutaneous human papillomavirus seroreactivity in basal cell and squamous cell carcinomas of the skin. J Infect Dis. 2012;206:399–406.
12. Lutzner M, Orth G, Dutronquay V, Ducasse MF, Kreis H, Crosnier J. Detection of human papillomavirus type 5 DNA in skin cancers of an immunosuppressed renal allograft recipient. Lancet. 1983;322:422–4.
13. Chen FP. Efficacy of imiquimod 5% cream for persistent human papillomavirus in genital intraepithelial neoplasm. Taiwan J Obstet Gynecol. 2013;52:475–8.
14. Connolly K, Manders P, Earls P, Epstein RJ. Papillomavirus-associated squamous skin cancers following transplant immunosuppression: one notch closer to control. Cancer Treat Rev. 2014;40:205–14.