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Acquired Epidermodysplasia Verruciformis Post-renal Transplant: A Case Report of Rare Manifestation of Immunosuppression

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Abstract

Acquired epidermodysplasia verruciformis (EV) is a rare dermatologic disorder linked to increased susceptibility to specific HPV infections in immunosuppressed states. We report a 43-year-old renal transplant recipient on prolonged immunosuppressive therapy with tacrolimus, mycophenolate mofetil, and corticosteroids who developed multiple asymptomatic wart-like papules and plaques on extremities, hypopigmented pityriasis versicolor-like macules on the trunk, and seborrheic keratosis-like lesions on the face. Histopathology confirmed EV, showing acanthosis, hyperkeratosis, and keratinocytes with pale blue cytoplasm, perinuclear halos, and mild nuclear dysplastic changes. Due to malignancy risk in sun-exposed areas, strict sun protection and follow-up were advised. With acitretin and imiquimod unavailable, lesions were managed with intralesional measles, mumps, rubella (MMR) vaccine, and topical keratolytic, resulting in partial regression. This case highlights the need for early recognition, vigilant monitoring, and tailored management of EV in immunosuppressed patients, emphasizing further research to refine therapeutic strategies in resource-limited settings.

Keywords: Acquired epidermodysplasia verruciformis; Epidermodysplasia verruciformis; Human Papillomavirus; Immunosuppression; Renal transplant.

Introduction

Epidermodysplasia verruciformis (EV) is a rare genetic condition, either sporadic or familial, first identified by Lewandowsky and Lutz in 1922.[1] Individuals with EV have a heightened susceptibility to specific beta-human papillomavirus (HPV) infections due to mutations in the EVER1 or EVER2 genes. Over 20 HPV types are linked to EV, including 3, 5, 8, 9, 10, 12, 14, 15, 17, 19, 25, 28, 29, 36, 47, 49, and 50.[2] EV often arises in childhood, typically as plane warts like lesions over hands and feet followed hypopigmented macules resembling pityriasis versicolor over the trunk and seborrheic keratosis-like plaques over the face.[3,4] HPV types 5 and 8 are mainly implicated in malignancy, most commonly squamous cell carcinoma (SCC), particularly in sun-exposed areas.[3] In 2009, Rogers et al., introduced "acquired EV" (AEV) to describe EV in HIV (Human Immunodeficiency Virus) infected and post-renal transplant patients.[5] EV occurs globally without gender or geographic bias. Its reported frequency is 11% in Europe and the USA and 40% in Japan, but it is rarely reported in countries of South Asian Countries.[3]

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Case Report

A 43-year-old Nepalese laborer, born of a non-consanguineous marriage, presented to the dermatology OPD with multiple asymptomatic grayish-white flat, round to irregular papules and plaques on the dorsum of hands and legs, multiple hypopigmented macules on the face, upper limbs, and trunk and blackish papules and plaques over the cheeks, neck, and forehead. These lesions started 3 years ago with a few flat papules on the extensor surface of the right leg, progressively increasing in number and size (0.5-1.5cm) with a rough surface and normal surrounding skin spreading to the left leg and dorsum of bilateral hands (Figure 1, 2). Within the same period, he developed irregular blackish papules and plaques over the beard area, which caused discomfort during shaving (Figure 3). Hypopigmented macules subsequently appeared on the neck, chest, shoulders, forearms, abdomen, and back, measuring 0.15-2.5 cm, round to oval, smooth surface with normal surrounding skin (Figure 4). Hair, nails, or mucosa were unaffected.

The patient underwent a left renal transplant 6 years back and was on maintenance immunosuppressive therapy, including oral tacrolimus (2 mg twice daily), mycophenolate mofetil (MMF) (500 mg twice daily), and prednisolone (20 mg daily). The skin lesions developed 3 years post-transplant. Patient had a history of pelvic bone tuberculosis 15 years earlier, treated with a 1-year course of anti-tubercular therapy. There was no history of diabetes, heart disease, thyroid disorder, or similar family conditions. Serological tests for syphilis, hepatitis B/C, and HIV were negative.

Skin biopsy from the lesion of the right foot revealed epidermis with hyperkeratosis, mild to moderate acanthosis, large keratinocytes with perinuclear halos and blue-gray cytoplasm along with mild dysplastic nuclear changes like irregular nuclear contours, pleomorphism, and atypia. The dermis showed fibro-collagenous tissue, mild lymphocytic infiltration, eccrine glands, and congested vessels (Figure 5, 6). Facial lesions could not be biopsied due to a lack of written informed consent. HPV typing was unavailable

Figure 1: Multiple grayish-white flat and verrucous papules and plaques over the dorsum of bilateral hands

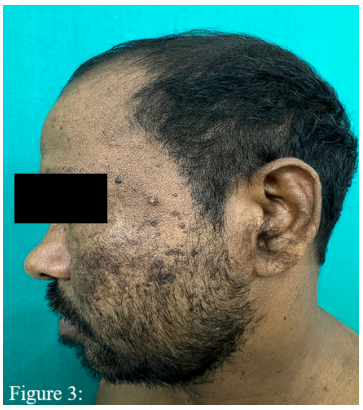

Figure 3: Multiple blackish hyperpigmented papules and plaques over the left cheek and forehead; similar lesions over the right cheek

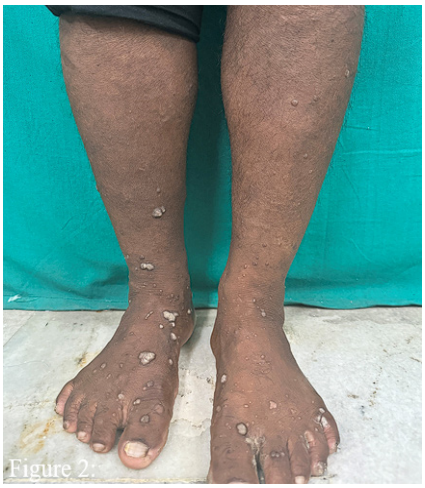

Figure 2: Multiple grayish-white flat and verrucous papules and plaques over the dorsum of bilateral legs and foot

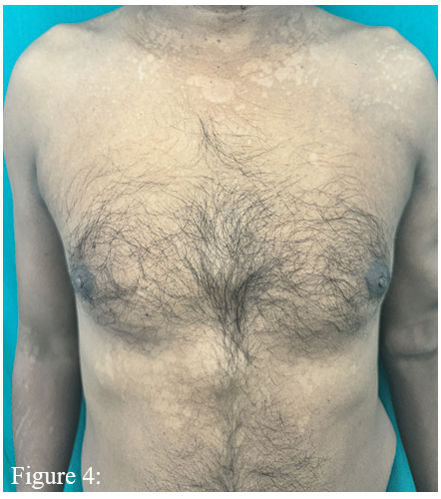

Figure 4: Multiple hypopigmented macules over the upper chest, abdomen, and right forearm

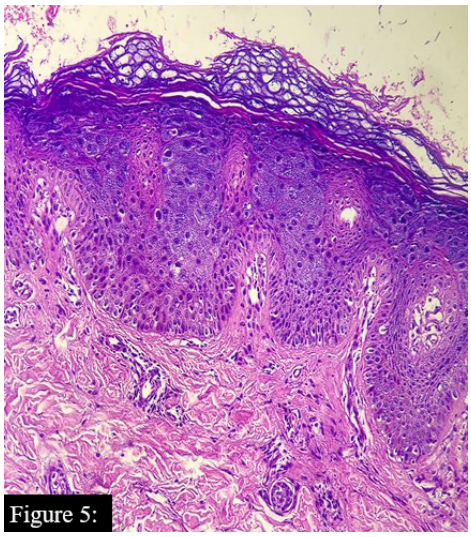

Figure 5: H&E stain 20X. Histopathology of verrucous papule shows epidermis with mild to moderate acanthosis and hyperkeratosis; dermis shows fibrocollagenous tissue and mild lymphocytic infiltrate

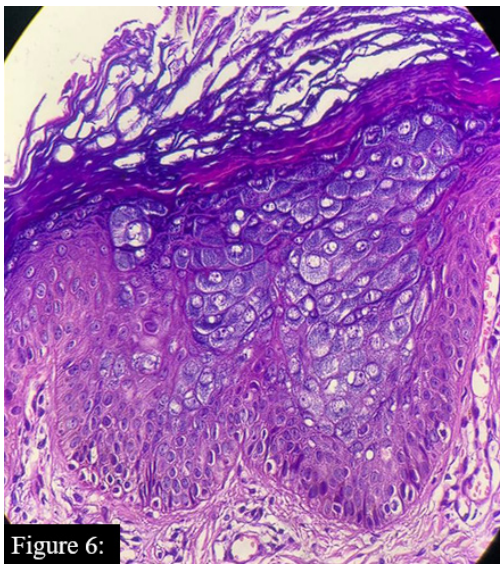

Figure 6: H&E stain 40X. Large keratinocytes with abundant blue-gray cytoplasm, perinuclear halos, irregular nuclear contours, atypia, and pleomorphism

in our setting. KOH mount from hypopigmented trunk lesions did not show the "spaghetti or meatballs" appearance of yeast and hyphae, ruling out pityriasis versicolor.

Verruca vulgaris was ruled out as there was no papillomatosis or koilocytosis in histopathology. Acrokeratosis verruciformis of Hopf was also ruled out as no hypergranulosis, elongated rete ridges, or papillomatosis resembling church spires were noted.

The patient was diagnosed as AEV based on the lesion's chronology, morphology, post-transplant immunosuppressive therapy history, and histopathology. The case was consulted with a nephrologist regarding drug modification and dose adjustment. Meanwhile, the treatment included intralesional injection of MMR vaccine over the largest verrucous lesion on the right leg and topical salicylic acid (40%). The injected lesion regressed, while the distant lesions remained unchanged. The patient was lost to follow-up, preventing further assessment and treatment.

Discussion

In 1922, Lewandowsky and Lutz first documented autosomal dominant EV.[1] The genetic basis of the disorder was established later. Mutations in EVER1/TMC6 and EVER2/TMC8, which regulate intracellular zinc levels in keratinocytes and immune cells, account for ~75.6% of cases. These mutations impair immune regulation, increasing susceptibility to HPV infections.[6] Six cases of autosomal dominant inheritance and five of X-linked inheritance have been reported.[7] EV remains exceedingly rare, with only 500 cases documented by 2017.[8]

In 2018, Huang et al., proposed a new classification system dividing EV into two categories: genetic and acquired. Genetic EV was subdivided into two types: i) classic EV: common with mutations in EVER1/TMC6 and EVER2/TMC8 on chromosome 17q25, accounting for most cases. ii) non-classic EV. Acquired EV was further categorized as secondary to i) viral infections and ii) iatrogenic immunosuppression, linked to immunosuppressive drugs used in organ transplantation therapies.[8,9]

Genetic EV appears early in patients with family history, especially in consanguineous families. Acquired EV, however, occurs later due to immunosuppression from HIV or immunosuppressives like tacrolimus, cyclosporine, corticosteroids, azathioprine, and methotrexate without any genetic link.[9] Our case highlights acquired EV due to prolonged immunosuppression with tacrolimus and MMF post-renal transplant consistent with some documented cases.[10,11] The exact mechanism remains unclear but likely involves broad immunosuppression, increasing susceptibility to HPV infections. Notably, EV lesions may persist even after stopping immunosuppressive therapy.[9]

HPV types 14, 20, 21, and 25 are linked to benign lesions, while types 5, 8, 10, and 47 are associated with malignancies in 90% of cases.[12] SCC can occur in 30–70% of cases, typically in the fourth or fifth decade in sun-exposed areas, implicating ultraviolet radiation as a co-carcinogen. Basal cell carcinoma (BCC) is less common.[13,14]

Classic EV histopathology shows mild to moderate acanthosis, hyperkeratosis, large cells with blue-gray cytoplasm, and perinuclear haloes due to underlying

HPV infection. Post-renal transplant patients often exhibit dysplastic nuclear changes like nuclear atypia and polymorphism.[15]

Treatment options, including electrodessication, cryotherapy, topical retinoids, contact sensitization, imiquimod, interferons, 5-fluorouracil, podophyllotoxin, topical cidofovir, and topical keratolytics like salicylic acid, have shown limited success in clearing lesions.[5,16] Stringent sun protection and lifelong monitoring for premalignant or malignant lesions are crucial. Malignant lesions require surgical excision, grafting, or local ablation. Acitretin (0.5–1 mg/kg/day) is the preferred drug, while topical imiquimod (five times weekly) has shown promising results. Surgical methods like electrosurgical removal and cryotherapy for benign or premalignant lesions remain palliative, with further studies needed to evaluate long-term efficacy.[3,17]

A case of acquired EV in a systemic lupus erythematosus (SLE) patient on azathioprine and prednisolone, which regressed when switched to MMF, but recurrence occurred when switched to methotrexate, has been described in the literature.[18] However, drug and dose modification studies in cases of acquired EV remain limited. In our case, there were ongoing discussions with the nephrologist regarding this issue, but the patient was eventually lost to follow-up, preventing the implementation.

Acitretin and imiquimod, first-line treatments are unavailable in Nepal. So, the patient was advised strict sun protection, and alternate therapies like intralesional MMR vaccine and keratolytic were used. Intralesional MMR, which is effective for viral warts, remains experimental for acquired EV secondary to immunosuppressives due to limited evidence. The unavailability of first-line agents necessitated its use.[19,20] Following treatment the patient showed partial response, with complete regression in injected lesions and reduced size in adjacent lesions, but no effect on distant lesions. Follow-up was advised for malignancy risk.

Loss to follow-up was a significant limitation, preventing long-term treatment outcome assessment and malignant transformation risk. Additionally, a biopsy of facial lesions could not be performed and lack of HPV typing tests hindered diagnostic confirmation. The unavailability of first-line treatments restricted management options.

Conclusion

Acquired EV is a significant concern in renal transplant recipients on long-term immunosuppressive therapy, with potential malignant transformation risk, commonly SCC. Early recognition and routine dermatologic surveillance are crucial for timely intervention. Moreover, strict sun protection is vital to reduce cancer risk. Further research is needed to establish standardized management protocols and explore immunosuppressive therapy modifications to minimize the risk of EV in transplant patients.

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