Nonpruritic hypopigmented macules on an immunocompromised patient

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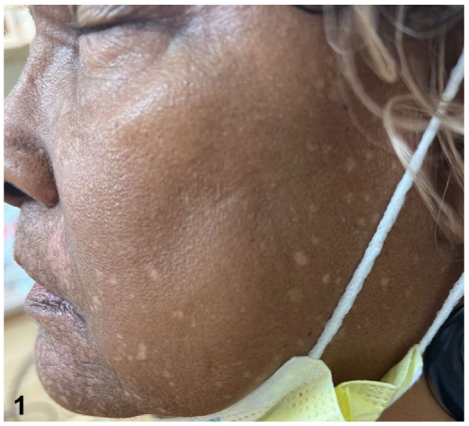

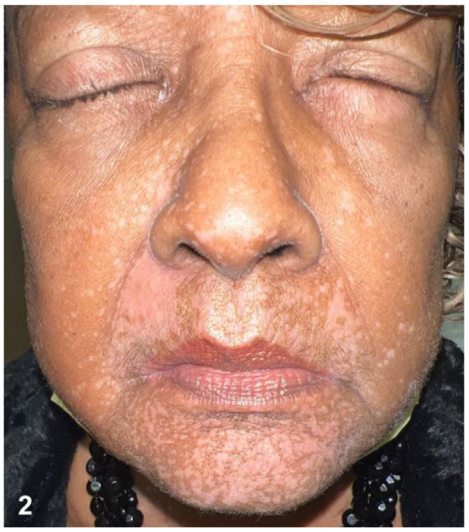

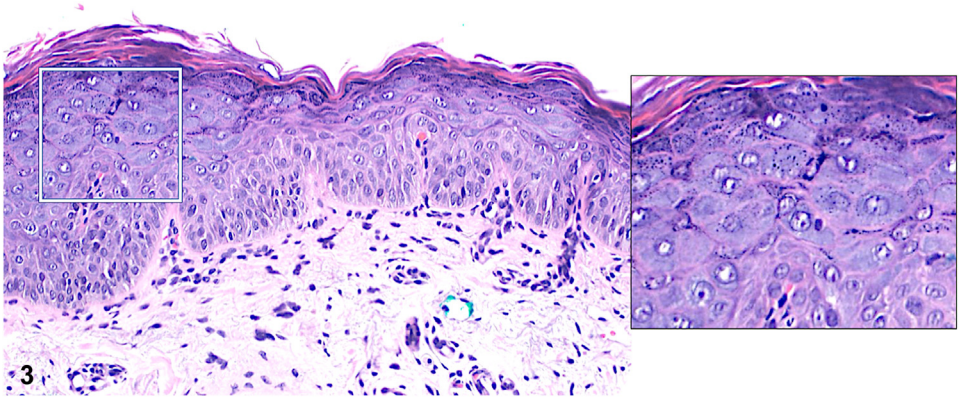

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A 67-year-old woman with a history of kidney transplantation on tacrolimus, mycophenolate, and prednisone presented with asymptomatic and hypopigmented skin lesions on her face, neck, and chest. The facial lesions first appeared 2.5 years prior but began spreading and increasing in size. Physical examination revealed numerous hypopigmented, polygonal, nonscaly macules and thin, flat papules distributed diffusely on the face, neck, and upper chest (Fig 1), with some coalescing into hypopigmented plaques in the perioral region (Fig 2). Shave biopsy revealed mild to moderate acanthosis, hyperkeratosis, and the presence of enlarged cells with blue-gray cytoplasm within the spinous layer (Fig 3).

Question 1: Which is the most likely diagnosis?

A. Acquired epidermodysplasia verruciformis (AEV)

B. Lichen planus

C. Pityriasis versicolor (PV)

D. Darier disease

E. Verruca plana

Answer:

A. AEV — Correct. AEV manifests with diffuse, polygonal, hypopigmented macules, papules, or plaques with a "flat wart"-like or PV-like appearance. Histological findings include epidermal acanthosis, hyperkeratosis, and enlarged cells with bluish-gray cytoplasm and cleared out nuclei, perinuclear halos, and variably prominent keratohyalin granules.[1-3] Epidermodysplasia verruciformis is a condition that can be inherited or acquired. In the acquired form, it affects patients with deficient cell-mediated immunity due to infection (eg, HIV), malignancy, medications, or organ transplantation.[2]

B. Lichen planus — Incorrect. Lichen planus is characteristically pruritic and pink or violaceous in color with overlying Wickham striae. Histopathologic findings include a lichenoid interface tissue reaction, a distinctive saw-tooth pattern, and hypergranulosis.

C. PV — Incorrect. PV presents with hypopigmented macules with fine, whitish scale. Yellow fluorescence on Wood's lamp test and the presence of hyphae and spores on KOH are typical.

D. Darier disease — Incorrect. Darier disease presents with small, symmetric, skin-colored to yellow-brown papules found in a seborrheic distribution. They are often greasy, firm, and emit a strong odor. Histopathology is characterized by acantholytic and dyskeratotic cells represented as "corps ronds and grains."

E. Verruca plana — Incorrect. Verruca plana are small flat-topped brownish or skin-colored papules mostly located on the face, back of the hands, and shins. These are commonly associated with human papillomavirus 3 (HPV-3) and HPV-10. Orthokeratosis, mild acanthosis, slight papillomatosis, and prominent koilocytes in the granular layer are typical features.

Question 2: What is the most commonly identified infectious agent associated with this disorder?

A. Epstein-Barr virus (EBV)

B. HPV

C. *Malassezia furfur*

D. HIV

E. Polyomaviridae

Answer:

A. EBV — Incorrect. EBV is a double-stranded DNA virus within the herpesvirus family that causes infectious mononucleosis and acute genital ulceration (Lipschütz ulcers). EBV is also associated with Burkitt lymphoma and nasopharyngeal carcinoma, among other malignancies.

B. HPV — Correct. HPV is a family of double-stranded DNA viruses, subdivided into groups. AEV is characterized by an unusual susceptibility to beta-HPV group viruses, which are nonpathogenic in immunocompetent hosts. The genus *beta-papillomavirus* (also known as beta) contains about 50 species differentiated by the DNA sequence of L1 gene. HPV5 and HPV8 have been detected in over 90% of cases of AEV.[2]

C. *Malassezia furfur* — Incorrect. This organism is part of the skin microbiome and is associated with the development of PV, *Malassezia* folliculitis, and seborrheic dermatitis.

D. HIV — Incorrect. While immunosuppression due to HIV renders hosts more susceptible to AEV, this virus is not the direct cause of the cutaneous infection.

E. Polyomaviridae — Incorrect. These viruses have been implicated in the development of Merkel cell carcinoma and pruritic and dyskeratotic

dermatosis in immunocompromised hosts, particularly solid organ transplant recipients.

Question 3: Which of the following statements relating to this condition is true?

A. Patients with this condition require regular skin examinations due to the increased risk of malignant transformation, most commonly melanoma

B. The utilization of HPV vaccination is currently Food and Drug Administration approved for the prevention of this condition in solid organ transplant recipients

C. Although this condition has been associated with HIV, lymphoma, leprosy, and iatrogenic immunosuppression, including cyclosporine and methotrexate, immunodeficiency is a requirement for diagnosis

D. Although described treatments include cryotherapy, laser ablation, topical and systemic retinoids, imiquimod, and 5-fluorouracil, no curative therapy has been discovered for the acquired or the inherited forms of this condition

E. The inherited form of this condition has been linked to mutations in the *EVER1* and *EVER2* genes, which code for transcription factors known to regulate gene expression in T-cell development

Answer:

A. False — HPV5 and HPV8 have greater oncogenic potential, leading to an increased risk of malignant transformation into squamous cell carcinoma.[2]

B. False — The HPV vaccine is not Food and Drug Administration approved for the treatment or prevention of AEV. One study reported on a positive outcome for a renal transplant patient for whom HPV vaccine was used as part of a multimodal regimen.[4] More evidence is required to support vaccination in this context.

C. False — The "acquired" form of epidermodysplasia verruciformis (AEV) occurs in individuals with a decreased cell-mediated immunity which allows for susceptibility to HPV.[2,5] AEV can affect both immunosuppressed (ie tumor necrosis factor α inhibitor use for psoriasis[6]) and immunocompromised patients; however, immune "deficiency" is not a requirement for disease.

D. True — Treatment of AEV is inconsistent and based largely on anecdotal evidence. Topical and systemic retinoids, such as tretinoin and acitretin, have been used with some success.[1,5] In transplant patients, changing immunosuppressive medications, specifically from azathioprine to mycophenolate mofetil, has also been proposed as a viable treatment recommendation.[2] Other treatments include glycolic acid 15%,[2,7] combination therapy involving glycolic acid and imiquimod,[1,2,5] high-dose oral cimetidine, and interferon.[3,7] In our case, dosage of acitretin 25 mg three times weekly (Monday, Wednesday, Friday) was started. Upon follow-up 3 months after initiating acitretin, the patient noted improvement.

E. False — Mutations in the *EVER1* and *EVER2* genes have been found in 50% to 75% of patients with inherited epidermodysplasia verruciformis. Although the exact mechanism of function of the EVER proteins is not fully understood, current evidence suggests a role in zinc homeostasis. In keratinocytes, both EVER1 and EVER2 were found to affect zinc distribution within the cell by physically interacting with zinc transporter 1. This complex negatively regulated zinc-stimulated transcription factors such as Elk and c-Jun, members of the AP-1 family.[8] Because zinc is used as a viral protein cofactor, and AP-1 is a key factor in HPV intracellular proliferation, any disruption in EVER proteins could potentially lead to a proliferative advantage for HPV.[9]

Abbreviations used:

AEV: acquired epidermodysplasia verruciformis
HPV: human papilloma virus
PV: pityriasis versicolor
EBV: Epstein-Barr virus

Conflicts of interest

None disclosed.

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