

# Epidermodysplasia Verruciformis and the Risk for Malignancy

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### PRACTICE POINTS

- Epidermodysplasia verruciformis (EV) is a rare genodermatosis that usually presents in early childhood and presents as verrucous papules and plaques most commonly on the skin of the head, neck, and upper extremities. It often is misdiagnosed as pityriasis versicolor.
- Mutations of the *EVER1* and *EVER2* genes have been identified as a source for developing EV.
- Epidermodysplasia verruciformis produces wartlike lesions in individuals who have a unique susceptibility to acquiring the human papillomavirus and early onset of nonmelanoma skin cancers, most commonly squamous cell carcinomas related to viral oncogenesis.
- Avoidance and protection from UV exposure is a critical component of treatment plans for patients with EV.

To the Editor:

Epidermodysplasia verruciformis (EV) is a rare autosomal-recessive genodermatosis characterized by widespread infection with specific strains of human papillomavirus (HPV). Patients with EV have a unique susceptibility to acquire HPV due to defects in cellular immunity to the presenting antigens.<sup>1</sup> These defects may be related to mutations of the *EVER* genes or due to acquisition of an immunosuppressive condition.<sup>2,3</sup> Infections with HPV-3 and HPV-10 do not lead to the development of malignancies. However, infection with HPV-5, HPV-8, and HPV-14 can lead to the development of nonmelanoma skin cancers, usually squamous

cell carcinomas (SCCs), in approximately 60% of patients.<sup>3,4</sup> This viral condition lasts throughout the patient's lifetime and presents as tinea versicolor-like macules and patches. These lesions may be confused with seborrheic keratosis or verruca plana.<sup>5</sup> Lesions typically are hypopigmented but occasionally may be hyperpigmented or erythematous. They often are found on the trunk, but lesions on the face, arms, palms, legs, and soles have been reported.<sup>5</sup> Mucous membranes are always spared. Epidermodysplasia verruciformis often presents in childhood, except in cases related to acquired immunosuppression. The condition has no sex or racial predilection and no geographical preference.<sup>5</sup>

A 7-year-old boy (Fitzpatrick skin type V) presented with an asymptomatic rash on the trunk (Figure 1), dorsal aspect of the hands, and forehead. The lesions first appeared 5 years prior on the upper back and upper chest and had recently spread to the forehead and frontal aspect of the scalp. The patient had a history of myelomeningocele, which was corrected at birth with surgical placement of a ventriculoperitoneal shunt. The patient was otherwise healthy and met all appropriate developmental milestones for his age group. Family history revealed consanguinity of the patient's paternal grandparents who were first cousins. The patient's

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**Figure 1.** An asymptomatic rash on the neck and chest.

mother denied any other family member having similar rashes or lesions.

The patient had been treated for pityriasis versicolor on and off for 2 years by another dermatologist. His mother reported faithfully applying ketoconazole cream twice daily for several months with no improvement. She also reported using topical steroids, which did not provide any benefit. The patient and mother denied any associated pruritus, bleeding, burning, or physical discomfort.

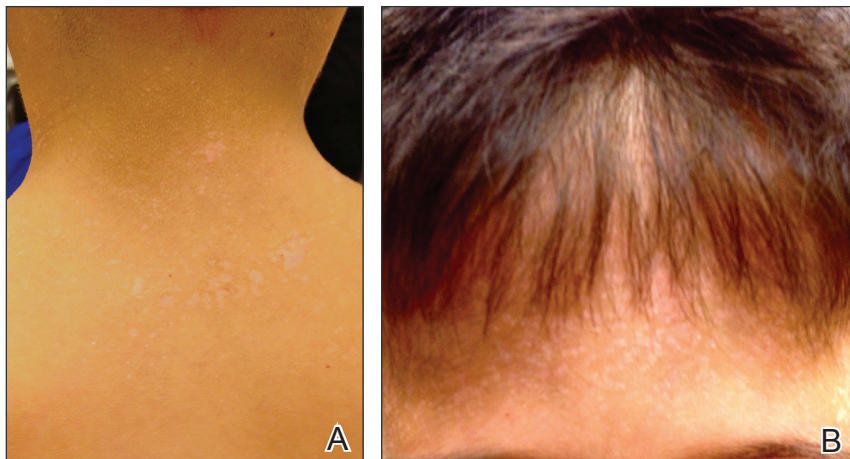
Skin examination revealed diffuse, flat, polymorphous, hypopigmented and salmon-colored hyperkeratotic macules and patches with mild scaling on the upper region of the anterior aspect of the chest and upper back (Figure 2A). Additionally, the patient had an extensive number of lesions on the forehead and frontal aspect of the scalp (Figure 2B).

A shave biopsy demonstrated a thick basket weave stratum corneum, koilocytes, and large pale keratinocytes with characteristic blue cytoplasm. These findings were characteristic for EV.

At the patient's 3-month follow-up visit, he again denied any symptoms associated with the lesions and reported that the appearance was diminishing in severity. On examination there was no evidence of SCC. The mother was advised to discontinue all topical treatments for the patient and return to the office every 3 to 6 months for regular skin surveillance. The mother was further advised to protect the patient from UV radiation with sunscreen and sun-protective clothing.

Epidermodysplasia verruciformis was first reported by Lewandowsky and Lutz<sup>6</sup> in 1922. This rare condition often presents in childhood and is characterized by a persistent HPV infection and an autosomal-recessive inheritance pattern. Reports in the literature frequently involve kindreds. Often, patients with EV have a family history of first-degree or second-degree consanguinity.<sup>7</sup>

The clinical presentation of EV often resembles a pityriasis versicolor-like eruption. However, pityriasis versicolor is less commonly seen in childhood and is more prevalent in patients aged 21 to 30 years, likely due to increased sebum production and changing hormone levels. Furthermore, it is unusual to see pityriasis versicolor affect the face and scalp.<sup>8</sup> Lesions of EV vary from hypopigmented and pinkish red macules to confluent patches and hyperkeratotic verrucalike lesions.<sup>3</sup> Clinical characteristics also may include dyschromic patches; lesions that resemble flat warts on the trunk, face, and distal arms; and/or lesions that appear similar to seborrheic keratoses on the dorsal aspect of the hands.<sup>9,10</sup>



**Figure 2.** Flat, polymorphous, hypopigmented and salmon-colored hyperkeratotic macules and patches with mild scaling on the upper region of the upper back (A) and an extensive number of lesions on the forehead and frontal aspect of the scalp (B).

Mutations of the *EVER* gene downregulate a cell's ability to adequately attack the HPV antigens.<sup>11</sup> Although some patients with EV are found to have mutations of the *EVER1* and *EVER2* genes, a notable portion of patients with EV lack these mutations. Three other causes of EV include acquisition of immunosuppressive conditions including lymphoma, solid organ transplant, and human immunodeficiency virus. If one suspects autosomal-recessive inheritance of EV, genetic testing such as polymerase chain reaction DNA fragment analysis can be performed to determine if there are mutations on the *EVER1* or *EVER2* genes.<sup>12</sup>

The inability of patients with EV to mount an immune response to multiple types of HPV increases the risk for developing cutaneous malignancies.<sup>7</sup> Additionally, it is known that UV radiation diminishes skin cell immunity, and the combination of EV and UV radiation further increases the risk for developing SCCs.<sup>11</sup> The development of nonmelanoma skin cancers usually occurs on sun-exposed skin 20 to 30 years after the onset of lesions, with the highest occurrence of SCCs presenting in the fourth decade of life.<sup>1</sup>

Protection from UV light exposure is critical to reduce the risk for malignancy. Treatment options for EV lesions have included topical imiquimod 5%, 5-fluorouracil, oral isotretinoin, and intralesional interferon alfa, but patients are often refractory to these interventions. Curettage, surgical excision, electrosurgery, and laser ablation can be effective for individual lesions but carry a greater risk for scarring.<sup>1</sup> Photodynamic therapy with aminolevulinic acid and blue light represents a promising option that deserves further study.

Epidermodysplasia verruciformis should be considered as a differential diagnosis in all patients presenting with disseminated lesions resembling pityriasis versicolor that are unresponsive to treatment. A biopsy will help to establish the diagnosis. Patients should minimize sun exposure and report any skin lesions that are changing in appearance.

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