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Case Report

Eyelid squamous cell carcinoma in the setting of epidermodysplasia verruciformis (EV) diagnosed by next-generation sequencing: A case report and literature review

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1. Introduction

Epidermodysplasia verruciformis (EV) is an extremely rare autosomal recessive genodermatosis with an estimated incidence of 1 in 1,000,000.[1] It is characterized by abnormal susceptibility to human papillomaviruses (HPV) and a high rate of progression to cutaneous malignancy, especially SCC, of sun-exposed skin.[2] Mutations in the transmembrane channel gene TMC6/EVER1 or TMC8/EVER2 create patient susceptibility to infections by HPV (mainly beta-HPV) and the development of EV-typical plane warts.[3] However, these deficiencies only account for 75% of affected individuals. Additional genes (MST-1,[4] RHOH,[5] IL-7,[6] and CORO1A[7]) result in extensive HPV replication and therefore manifest with an EV-like phenotype.[2] EV is the first disease to correlate skin cancer and viral infection which serves as the cornerstone to the understanding of viral oncogenesis.[1,8] Ocular or orbital involvement of EV has not been reported previously. Here we report the clinical, histopathologic, and genetic findings, as well as management of a 41-year-old male presenting with an eyelid tumor subsequently identified as EV.

2. Case presentation

Here we report the clinical, histopathologic, and genetic findings, as well as management of a 41-year-old male presenting with an isolated eyelid tumor subsequently found to have epidermodysplasia verruciformis. To the best of our knowledge, this report represents a unique presentation of an isolated eyelid mass as the manifestation of epidermodysplasia verruciformis without obvious vegetating hyperkeratotic masses.

A 41-year-old Asian male presented with a left upper eyelid mass for one year associated with multiple pigmented maculopapules on his face (Fig. 1). The patient reported a history of painless, recurrent ulceration and crusting of the lesion. He denied a history of red eye, photophobia, or other symptoms. The slit lamp examination of the eye was unremarkable. Around age six, the patient spontaneously started to have disseminated, bean-sized, pinkish flat papules on his forehead, with adhesive scales on the surface without exudation, erosion, or pruritus. He also reported the gradual development of reddish flat papules on other regions. Around 7 years prior to presentation, he started to have multiple brownish pigmented flat papules and had several excisional biopsies of the scalp, chest and face region which were diagnosed as squamous cell carcinoma (SCC). These medical records were unclear since the patient had these treatments while abroad. The dermatologist suggested possible xeroderma pigmentosum (XP) based on skin lesions. His parents were close relatives (details unknown); all other family members including his sibling and children were in good general health.

The oculoplastic surgeon resected the lesion (seen in Fig. 2), followed by eyelid reconstruction. The resected tissue was submitted for histopathological and genetic analysis. Histopathologic examination was consistent with SCC (Fig. 3). Additionally, DNA sequencing (Fig. 4) demonstrated homozygous TMC8 gene mutation indicative of Epidermodysplasia Verruciformis (EV).

The patient was referred to dermatology for systemic workup. Biopsies by the patient's dermatologist identified multiple skin malignancies including SCC, basal cell carcinoma (BCC), seborrheic keratosis, and actinic keratosis on several regions of the body. Two years later, the patient developed SCC in the same region again and underwent orbital exenteration with free flap and radical neck/axillary dissection.

3. Discussion

There are several treatment choices for ophthalmologists when we meet a patient with eyelid neoplasm. Given his previous history of SCCs,

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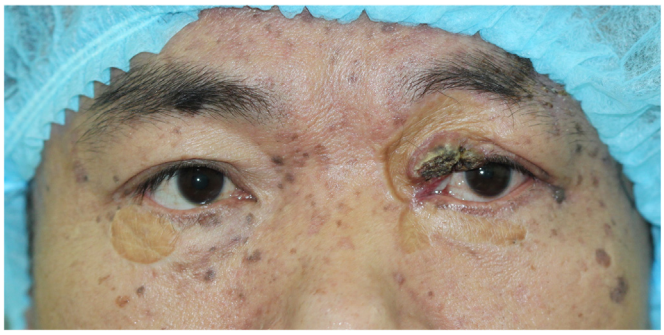

Fig. 1. The left upper eyelid mass with multiple pigmented maculopapules on the face.

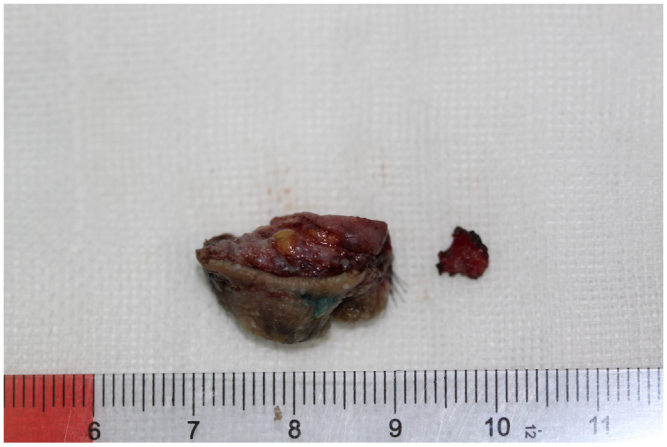

Fig. 2. Intraoperative specimen of left upper eyelid mass.

the newly occurred eyelid mass was most likely to be SCC again. Cryotherapy is a good treatment for the precancerous conditions of SCCs like actinic keratosis with an average recurrence around 0.8%.[9] And it's mostly used in low risk or benign lesions less than 2 cm in diameter. The tumor was resected and sent for histopathological examination. The histopathological and genomic analysis seemed most likely to determine the cause and treatment options. Genomic analysis was indicated to determine the etiology of the disseminated papules throughout the patient's body, allowing his physicians to better treat his chronic skin issues. Advise the patient to avoid UV-exposure, and add vitamin supplements; prescribe topical ointments containing etretinate or 5-fluorouracil are the supportive treatments for EV but aren't the most proper next step prior to confirmation of the diagnosis[1]; furthermore, these interventions are not appropriate for the management of a malignant cancer secondary to EV.

The differential diagnosis in our case should focus on systemic disease rather than individual eyelid malignancy, considering disseminated cutaneous lesions around the whole body. SCC is the second most common eyelid carcinoma in Caucasian people and the third in Asian population. But notably, patients with eyelid malignancy like BCC, SCC and malignant melanoma are the elderly with the median age all over 60–70 years,[10] very rare will have such early onset like our case. The most common syndromes associated with multiple squamous cell carcinomas are: xeroderma pigmentosum, Ferguson-Smith, Muir-Torre syndrome, Mibelli-type porokeratosis, keratitis-ichthyosis-deafness syndrome, Rothmund Thomson syndrome, Bloom syndrome, and epidermodysplasia verruciformis.[11] The presumed diagnosis by the patient's dermatologist, XP, is a genodermatosis caused by genetic deficiency affecting DNA repair mechanisms which also could occur in early childhood with pigmentary cutaneous changes. However, almost all

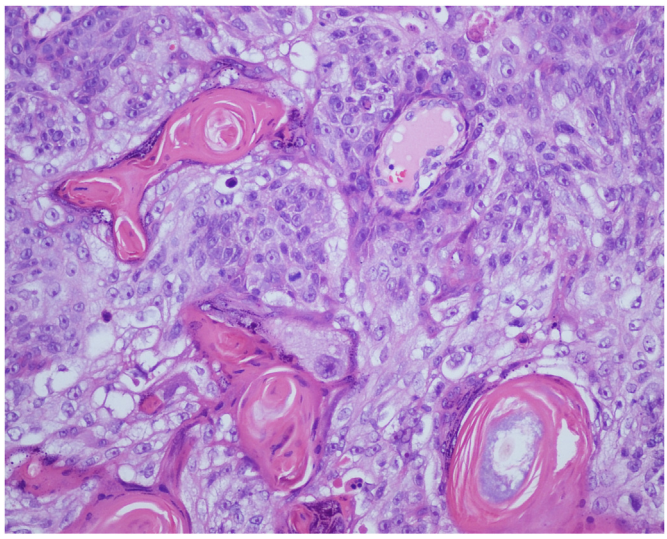

Fig. 3. Histopathologic image of the eyelid lesion.
The lesion was epithelial neoplasm characteristic of squamous cell differentiation with marked keratin pearls, intercellular bridge and enlarged nucleoli, suggestive of well differentiated squamous cell carcinoma. The tumor was arranged in closed nests without basal cell palisading feature and involved superficial dermis. (original magnification ×200, hematoxylin and eosin stain).

children with XP would develop freckling of the skin in sun-exposed areas by age 2. About half patients develop first skin cancer by age 10, which is much earlier than our case, though there're reports that XP in the Chinese population may have a later age of onset with milder symptoms.[12] A vital difference is that approximately 40% of patients with XP suffer from ophthalmological problems including photophobia, conjunctivitis and corneal abnormalities.[13] Disseminated superficial actinic porokeratosis (DSAP) also could present with multiple scaly patches in sun-exposed areas. But unlike EV or XP, DSAP usually starts during the third or fourth decade of life and rarely affects children and exhibits seasonality with less prominence in the winter. Most lesions of DSAP are benign, very occasionally may develop SCC or Bowen's disease.[14] The best and most precise diagnostic approach still relies on genetic examinations rather than clinical or histopathological findings.

To the best of the authors' knowledge, this is a rare case of eyelid EV with limited previous report.[15] Epidermodysplasia verruciformis, known as tree man disease, has EV-typical plane wart: a macular rash similar to that of pityriasis versicolor associated with verrucous scaly papules.[1] Signs commonly appear between the ages of 4 and 8, and most often before the age of 20, but later presentations may occur. It is characterized by the appearance of scaly macules and sometimes exuberant pseudotumoral papules, mainly on the hands and feet.[16] Notably, genetic alterations alone did not adequately explain the propensity for EV to arise in immunocompromised hosts, especially those who have undergone transplantation or who were positive for human immunodeficiency virus (HIV). Rogers et al.[17] firstly termed it as acquired epidermodysplasia verruciformis (AEV) or atypical EV. Classifying cases as genetic or acquired EV is the novel research focus.[18]

The treatment of EV is usually unsatisfactory and no curative therapies are presently available. A host of medications traditionally used to treat warty lesions have been used with variable results and limited success.[19] Therefore, early diagnosis, education of the patient, strict avoidance of UV exposure and excision of the tumoral lesions to prevent the development of malignancy are crucial.

4. Conclusions

This patient highlights the importance of differentiating common

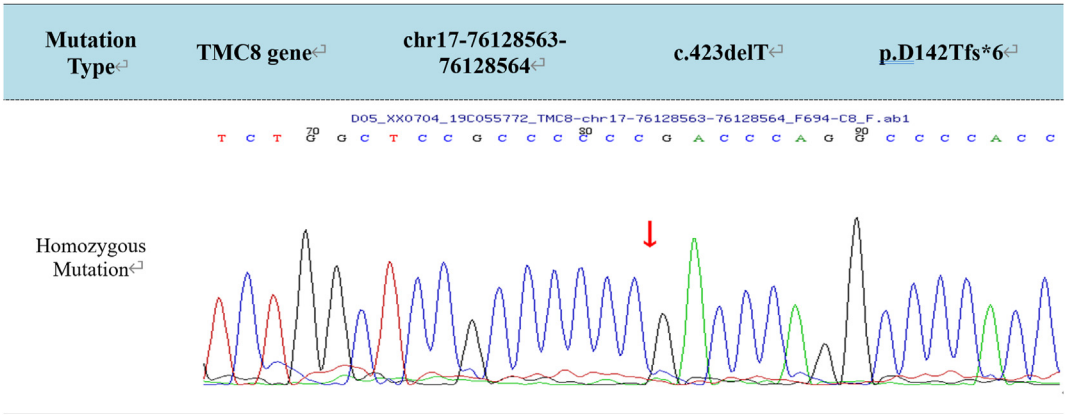

Fig. 4. Sanger sequencing validation of the next generation sequencing (NGS) variant.
Sanger sequencing was implemented to validate the possible gene mutations selected by NGS. The red arrow bar refers to the homozygous mutation of TMC8 gene which is indicative of epidermodysplasia verruciformis.

isolated eyelid malignancy from more serious systemic causes. Age of onset, combined ophthalmological problems, extraocular manifestations are useful for tentative diagnosis, but the ultimate diagnosis still relies on tissue biopsy with histopathological and genetic analysis.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that involved human patients or animals was conducted with the ethical approval of all relevant bodies and the study was performed in accordance with the Declaration of Helsinki,and the protocol was approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (ZJU-2)(approval number: No. Y2019-195)

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: LW, JY; Data collection: AS, HZ; Analysis and interpretation of results: HF, AS, LW; Drafting the manuscript: HZ, LW; All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

EV	Epidermodysplasia verruciformis
HPV	Human papillomaviruses
SCC	Squamous cell carcinoma
BCC	Basal cell carcinoma
XP	Xeroderma pigmentosum
DSAP	Disseminated superficial actinic porokeratosis
HIV	Human immunodeficiency virus
AEV	Acquired epidermodysplasia verruciformis

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2022.100066.

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