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Case Report

Dermatology Section

A Rare Case of Epidermodysplasia Verruciformis with Non Syndromic Hearing Loss

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ABSTRACT

The onset of Non Syndromic Hearing Loss (NSHL) typically occurs without any other symptoms and can vary from person to person, even within the same family. Hearing loss can be unilateral or bilateral and can range from mild to profound degrees of hearing loss. Epidermodysplasia Verruciformis (EDV) is a dermatologic condition in which patients show reduced immunologic ability to defend and eradicate certain types of Human Papillomavirus (HPV), leading to persistent infection and an increased lifetime risk of developing cutaneous dysplasia and malignancy. Both conditions have a genetic background. However, their concurrent occurrence is very rare. Therefore, a case study is presented of a four-year-old female child who visited the dermatology outpatient department with a chief complaint of hearing loss and white-coloured lesions covering her arms, neck, back, and chest for the last two years. The hearing loss was gradual, not apparent at birth, and progressed slowly to complete hearing loss. A final diagnosis of EDV with Non Syndromic Sensorineural Hearing Loss (NSSNHL) was made based on clinical and histological examination.

Keywords: Bilateral hearing loss, Gene mutation, Hypopigmented macules, Inherited disorder, Pityriasis versicolour, Vitiligo

CASE REPORT

A four-year-old girl presented to the Dermatology outpatient department with the chief complaint of white lesions on the skin of her neck, back, chest, and arms for two years. The skin lesions initially appeared on the neck and gradually progressed to the chest, trunk, and arms, respectively. The patient did not exhibit scaling, itching, or photosensitivity, and the lesions progressively grew in number but not in size, with no history of similar episodes in the past. Over time, she also experienced gradually progressive hearing loss, eventually leading to total hearing loss. The hearing loss was not present at birth. The patient did not display any other symptoms, including ear pain, ear discharge, or fever, indicative of ear infections. No similar complaints were noted in the family. She was otherwise systemically healthy, with no past history of surgeries or trauma. On physical examination, multiple hypopigmented macules of approximately 0.2-0.3 cm were observed on the neck, chest, back, and arms, which were not associated with scaling [Table/Fig-1a-c]. No mucosal or genital involvement was observed.

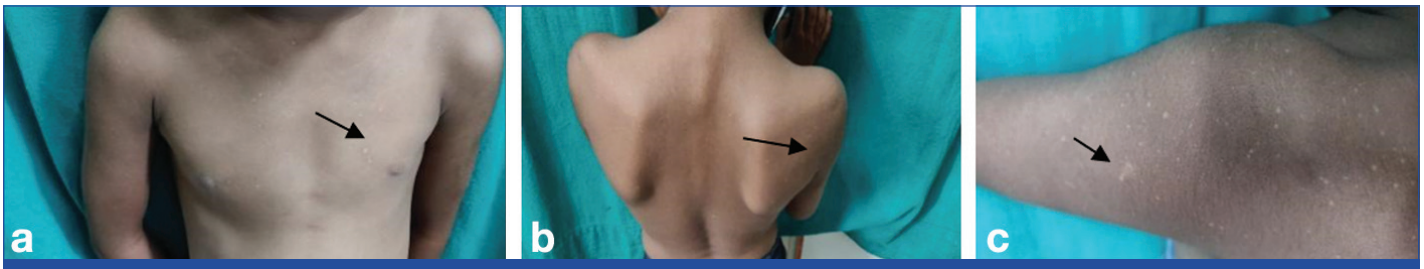
A probable diagnosis of vitiligo, pityriasis versicolour, squamous cell carcinoma, actinic keratosis, and seborrheic keratosis was established based on the clinical symptoms. Based on the Wood's Lamp test, vitiligo and pityriasis versicolour were ruled out due to negative accentuation and fluorescence.

KOH mount: Pityriasis versicolour was ruled out by microscopic analysis of scales soaked in potassium hydroxide, as the scales did not exhibit the characteristic grape-like clusters of yeast cells and lengthy hyphae.

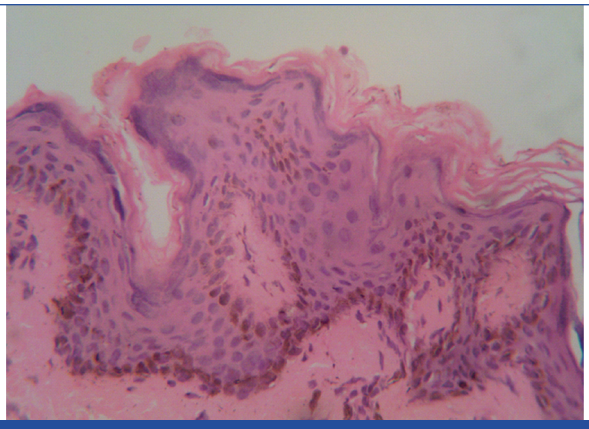
The likelihood of actinic keratosis, seborrheic keratosis, and squamous cell carcinoma, which often develop solitarily and at a later stage of life, was eliminated due to the multiple and early occurrence of lesions. A punch biopsy measuring 0.5*0.5 cm was taken from the affected area, which on histopathological staining revealed clear cells in both granular and spinous layers with a few enlarged atypical nuclei showing hyperchromatism, giving a characteristic basket weave appearance. The histopathological findings was suggested as EDV [Table/Fig-2].

Brainstem Evoked Response Audiometry (BERA): Brainstem Evoked Response Audiometry (BERA) was conducted, showing evidence of V wave formation noted at 80 dB on the left-side and 90 dB on the right-side, suggestive of bilateral sensorineural hearing loss [Table/Fig-3]. Therefore, a final diagnosis of EDV with NSSNHL was made based on clinical, histopathological, and BERA assessment.

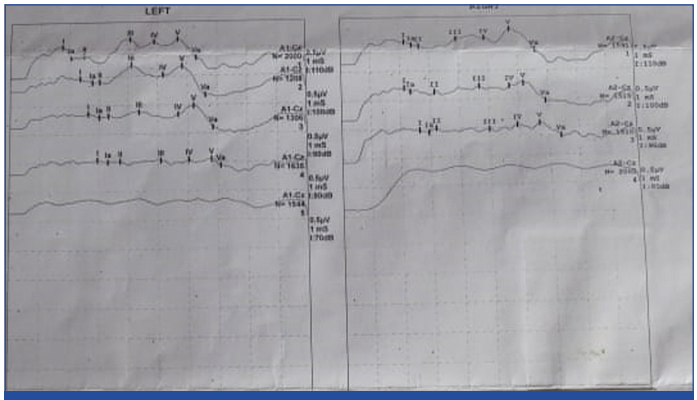
Initially, the patient was given oral etretinate (10 mg/day), but the affected skin began to burn and the lips became dry. Consequently, a six-month alternate treatment plan involving the topical use of 1-α, 24-dihydroxyvitamin D3 ointment (tacalcitol, Bonalpha) was selected. Strict photo protection was prescribed for the patient. The patient's guardian was also informed about how genetic counselling relates to autosomal recessive traits, the risk associated with parental consanguinity, and reports of autosomal dominant mode of inheritance. However, the diagnosis was not confirmed with genetic mapping in the present case due to the patient's financial constraints and the unavailability of genetic analysis. Therefore, the diagnosis was made based on the clinical and histopathological features.



[Table/Fig-1]: Demonstrating hypopigmented macules on (a) Chest; b) Back; c) Right arm.



[Table/Fig-2]: Showing hyperkeratosis, hypergranulosis, koilocytes and increased basal pigmentation (H&E, 100x).



[Table/Fig-3]: BERA report showing V^{th} wave formation at 80dB on left-side and 90dB on right-side.

Treatment options for hearing loss were discussed with the parents and medical decision-makers. The possible treatment options offered were continued observation with no intervention, Contralateral Routing Of Signals (CROS) hearing aid, bone conduction hearing implant, or a cochlear implant. Ultimately, after a shared decision-making process, the patient and family selected a CROS hearing aid.

Currently, the patient was lost to follow-up. However, upon further communication with the girl's parents, they reported that no new lesions were observed, the number of lesions reduced gradually, and she adapted well to the hearing aid.

DISCUSSION

Genodermatosis, also known as EDV, is rare to inherit. Individuals with this condition develop flat wart-like sores and pityriasis versicolour when exposed to EDV-HPV infections [1]. Lewandowski and Lutz were the first to describe this condition [1]. Approximately, 7.5% of cases manifest in infancy, 61.5% in children aged 5-11 years, and 22.5% in puberty. The disease shows an equal predilection for both genders and people of all races [2]. Tinnitus, vertigo, and abrupt hearing loss are some symptoms of Syndromic Sensorineural Hearing Loss (SSNHL). Only 10% of SSNHL cases have a known cause, and most cases lack sufficient information [3]. Numerous factors, including viral infections and autoimmune illnesses, are implicated among the known causes [4,5]. SSNHL is considered uncommon, with an estimated incidence rate of 5-30 occurrences per 100,000 people annually in the US. It tends to affect individuals between the ages of 30 and 60 years, and its occurrence rises with age. It is more common in men than in women. Though rare, reports of children being affected by this condition, with an incidence rate of 4.4-13.7%, are often associated with an unknown origin and a low chance of hearing recovery [6,7]. Hearing issues in EDV have rarely been documented in the literature. Al Rubaie S et al., described two instances of EDV in the literature, involving a sister and brother aged 14 and 18 years, respectively. The children had sensorineural deafness, neurological symptoms, and traditional skin lesions [8]. Karrabi M et al., reported on a nine-year-old boy who had sensorineural hearing loss and EDV [9].

EDV is generally inherited in an autosomal recessive manner, but X-linked recessive and autosomal dominant inheritance patterns have also been reported. Biallelic null variants in Transmembrane Channel-like (TMC)6 and TMC8, encoding EVER1 and EVER2 (Epidermodysplasia Verruciformis Enhancing Region) genes, account for 50–60% of EDV cases worldwide. It has been observed that germ line mutations in the TMC gene family at the DFNA36 and DFNB7/B11 loci, respectively, on chromosome 9q13–q21 have been identified as the cause of both dominant and recessive NSSNHL [10,11]. The collateral finding of EDV and NSSNHL was studied by Keresztes G et al., and Kurima K et al., revealing that the EVER1 and EVER2 genes are part of the TMC family, which consists of eight genes encoding trans membrane proteins with 6-10 domains [12,13]. Both studies demonstrated that the EVER1 and EVER2 genes are identical to the TMC6 and TMC8 genes, respectively. The expression of the TMC domain in the inner ear's cochlear hair cells could lead to hearing loss if there is a mutation in any of the 120 amino acid TMC proteins.

Currently, there isn't a targeted, efficient treatment for EDV. Pharmacologic therapies such as cimetidine, immunotherapy, imiquimod, and interferon, oral and topical retinoid have shown conflicting results. Preventive techniques including genetic counselling, photo protection and symptom monitoring to identify premalignant and malignant lesions earlier with the hope of controlling EDV and preventing benign lesions from progressing into cancer have been suggested in the literature, which was followed in the present case as well. The recommended medication at this time is acitretin, 0.5-1 mg daily. Two sisters with an autosomal recessive pattern experienced a quick reduction in the size of their cutaneous lesions when they were administered oral retinoid (0.5 mg/kg); however, a year later, the lesions relapsed [14]. There are several treatment options available for EDV, but patient education, prompt diagnosis, and removal of premalignant and malignant lesions are the most crucial. Due to their increased risk of developing such lesions, individuals with EDV require ongoing routine follow-up care. Recent research on the management of sensorineural hearing loss has identified corticosteroids as the cornerstone of care, demonstrating their ability to enhance patient outcomes. However, corticosteroids are typically recommended for acute management, expected to last a few days to a few weeks rather than months or years. Other acute treatment approaches, including immunoglobulin therapy and antiviral medication, have shown inconsistent evidence with varying effects [15,16].

In similar circumstances where an autoimmune disease is suspected, healthcare providers may suggest immunoglobulin treatment or plasma pheresis. However, there is limited evidence in the literature to support this type of treatment, and it is rarely performed. These are factors to consider during the acute phase, which were not taken into account in our circumstances. Treatment options are limited, especially for paediatric patients who may not seek treatment within the designated time frame. In such cases, non steroidal treatments are the only available options, with none showing significant efficacy. Evidence-based recommendations for clinicians treating paediatric patients with significant bilateral hearing loss, particularly those with acute hearing loss, normal imaging, and long-term care are lacking. Implants and assistive technology for hearing can be compensatory therapies that offer some relief and reduce residual handicap. However, they do not address the underlying problem or restore sound transmission in the damaged ear. More research is needed on the management of chronic sensorineural hearing loss to improve patient outcomes and prevent complications [3,15,16].

CONCLUSION(S)

In the above case, two disorders presenting simultaneously was observed: hearing loss and EDV, which is a rare occurrence. Therefore, considering their genetic linkage, whenever a patient presents with either of these disorders, it is suggested to check for other systemic conditions as well. There is no definitive therapy for EDV; however, early diagnosis, sun protection, lifelong monitoring for malignant transformation, and excision of cancerous lesions are crucial for better survival.

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