Abstract

Epidermal nevi are hamartomatous lesions that are typically present at birth, but can occur anytime during childhood and may rarely appear in adulthood. An estimated one-third of individuals with epidermal nevi have involvement of other organ systems; hence, this condition is considered to be an epidermal nevus syndrome. There are four distinct epidermal nevus syndromes recognizable by the different types of associated epithelial nevi: linear sebaceous nevi, linear nevus comedonicus, linear epidermal nevus, and inflammatory linear verrucous epidermal nevus (ILVEN). Each type may be regarded as a part of a syndrome with other systemic manifestations. We report a rare case of ILVEN syndrome in a 23-year-old female patient with a wide spectrum of mucosal, cutaneous, and skeletal abnormalities, demonstrating the polymorphic presentation of this condition.

Keywords: Alopecia cutis, bifid uvula, enamel hypoplasia, pruritic epidermal nevi, spina bifida

Introduction

Epidermal nevi are defined as congenital malformations or hamartomas derived from embryonic ectoderm. Epidermal nevi are further classified into variants according to the predominant epidermal structure involved, their clinical appearance, distribution, and the extent of their involvement. Lesions are usually noted at birth or infancy and are usually non-familial. Linear verrucous epidermal nevi clinically appear as verrucous papules and plaques distributed in a linear pattern following Blaschko’s lines (purported embryonic lines of ectodermal cleavage). Their extent varies from unilateral involvement (nevus unis lateralis) to extensive bilateral involvement (ichthyosis hystrix). Prevalence of linear verrucous epidermal nevus is estimated to be 1:1000 live births. In addition, they are associated with central nervous system (CNS) and or skeletal abnormalities. Oral mucosal lesions have rarely been documented.

Inflammatory linear verrucous epidermal nevus (ILVEN) is a rare variant of epidermal verrucous nevus that commonly affects females. Clinically, this condition is characterized by the appearance of recurrent inflammatory phenomena, with chronic eczematous or psoriasiform aspects, usually unilateral, with severe pruritus, and refractory to therapy. We report a rare case of ILVEN syndrome with a wide spectrum of cutaneous, mucosal, and skeletal abnormalities, demonstrating the polymorphic presentation of this condition.

Case Report

A 23-year-old female patient reported to the Department of Oral Medicine and Radiology with the chief complaint of bleeding gums since 6 months. The past medical history and family history were insignificant. The girl was the product of an uncomplicated term pregnancy, born by vaginal delivery. General examination revealed presence of scoliosis and asymmetrical legs (right leg and foot shorter than the left), due to which she had limping gait. Her right leg showed anterior bowing on the shin region. She also exhibited a patch with alopecia on the right fronto-parietal region suggestive of alopecia cutis. She also presented with dark brown pruritic papules that had linear pattern of distribution, limited to the right upper part of her body, involving neck, axilla, chest, back, shoulder, and right arm on which the lesion extended, streaking down the extensor surface to the nail of the little finger and thumb. Lesions present on the neck, axilla, chest, and back were dark and mossy in appearance. On the face, verrucous papules were present on the right side, involving the external ear and preauricular region, extending to the right cheek. Papules were also present on the forehead, originating from the scalp adjacent to midline, extending linearly downwards along the root of the nose, right nostril, to the vermilion border of the upper lip on the right side [Figure 1].

Intraoral examination revealed a diffuse, sessile, linear
papillary lesion on the dorsal surface of the tongue on the right side. Bifid uvula was also seen [Figure 2]. Generalized gingival inflammation was present with desquamation in relation to 12, 13, and 41 teeth region. The 13, 14, and 41 showed enamel hypoplasia and caries with 27 and 37 [Figure 3].

Panoramic radiograph showed the absence of 38, 47, and 48, and deviated nasal septum towards the right side. Axial CT scan of the brain showed a small calcific foci at right fronto–parietal region and the presence of radio-dense areas of fat deposits on bilateral cerebello–pontine cistern angle, suggestive of intracranial lipomas. Radiograph of the lumbar spine showed the presence of mild scoliosis with congenital schmorl's node at D–12, L–3, L–4, and L–5, and also the presence of spina bifida [Figure 4]. Anteroposterior and lateral view radiograph of right tibia–fibula showed sclerosis and anterior bowing of the tibia bone. On the basis of typical presence of unilateral pruritic linear epidermal nevi, bifid uvula, hypoplastic enamel, alopecia cutis, skeletal defects such as spina bifida, intracranial lipomas, and calcification, a diagnosis of ILVEN syndrome was given. As the patient was not ready for any interventional procedures, she was kept under follow-up.

**Discussion**

ILVEN is a variant of verrucous epidermal nevus and was originally described by Unna in 1896.\(^7\) It is characterized by recurrent inflammatory phenomena with chronic eczematous or psoriasiform aspect. ILVEN is caused by somatic mutations that result in genetic mosaicism and, although its physiopathology is still unclear, it is believed that it may be associated with an increase in the production of interleukins - 1 and 6, tumor necrosis factor-alpha, and intercellular adhesion molecule 1. Children are more commonly affected and it predominates in females in the ratio of 4:1. Most cases are sporadic, although familial cases have been reported. Clinically, it presents with erythematous and verrucous papules with intense pruritus and linear distribution following Blaschko’s lines. Although cases of bilateral involvement have been described, the disease is often unilateral and localized to one extremity. Oddly, the

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**Figure 1:** Frontal view of patient showing dark brown papules having linear distribution, limited on the right side of the face

**Figure 2:** Intraoral photograph showing bifid uvula

**Figure 3:** Intraoral photograph showing desquamative gingivitis and enamel hypoplasia in relation to 13 and 42

**Figure 4:** Radiograph of the lumbar spine showing mild scoliosis with congenital Schmorl’s node at D–12, L–3, L–4, L–5 (red arrow), and spina bifida (yellow arrow)
left leg is more affected. The classical clinical criteria for diagnosis of this condition was suggested by Altman and Mehregan in 1971 and later modified by Morag and Metzker in 1985, viz. early age of onset, predominance in females, frequent involvement of the left leg, pruritus, distinctive psoriasiform appearance, and marked refractoriness to therapy.

Aplasia cutis congenital is a cutaneous defect, usually involving the midline of the scalp, and can be seen associated with epidermal nevus syndrome (ENS). This condition typically presents as a solitary, hairless, well-margined skin lesion. Skeletal abnormalities are common in 50–66% of patients. Primary osseous changes include incomplete development of various bones, vertebral defects, campotodactyly, clinodactyly, abnormal clavicles, asymmetry of ribs, shortening of limb bones, posterior luxation of ankles, and asymmetry of the skull. Secondary bone changes include kyphoscoliosis and limb hypertrophy. Radiologically, there may be expansile lesions, thickening of the cortex, trabeculation of the bone (varying from radiolucent areas to uniform “ground glass” appearance), sclerosis, and deformities of the bone.

CNS involvement in ENS is estimated to occur in 50–70% of patients. Seizures and mental retardation are the most common neurological abnormalities in ENS. Other neurologic manifestations reported include hypotonia, hyperkinesia, hemiparesis, cranial nerve palsies, hydrocephalus, hemimegalencephaly, cortical lesions, cortical atrophy, ventricular abnormalities, and intracerebral calcification. Booth and Rollins in 2002 had reported intraspinal lipoma in ENS; however, intracranial lipoma has not been reported until 2006. They reported left orbital and left cerebello–pontine angle cistern lipomas, whereas in the present case, intracranial lipomas were present at the right and left cerebello–pontine angle cistern. Ocular defects associated with this syndrome include astigmatism; choriostomas; colobomas of eyelid, iris, choroid, and retina; cortical blindness; nystagmus; oculomotor dysfunction; optic nerve dysfunction; ptosis; and strabismus.

Oral involvement is a rare manifestation. Clinically, these lesions have been described as unilateral or midline papules or nodules with a papillary or verrucous surface. These lesions are found on one side of the body and characteristically they do not cross the midline. They have been found on the lips, tongue, buccal mucosa, and hard and soft palate, as well as on gingiva. In a review of 24 cases, Brown and Gorlin found that the majority of cases were on the left-hand side of the body. They also found that the most frequently affected intraoral sites were the lips, tongue, and palate, and less commonly the buccal mucosa, gingiva, tonsils, and pharynx. In five of the 24 cases, they found tooth abnormalities consisting of missing teeth, impacted teeth, abnormal spacing, and abnormal size. Teeth were frequently hypoplastic and few of the cases had reported odontodysplasia. Clinically, they described the intraoral lesions as wart-like, condylomatous, mammilated, or verrucous and ranging in color from that of normal oral mucosa to yellow-white, tan, dark brown, or gray. In contrast to this review, our case presents more often on the right side.

The histopathologic features of epidermal nevi include moderate hyperkeratosis, anacanthosis, papillomatosis in psoriasiform pattern, and dermal infiltration or even Munro’s micro-abscesses. The rete ridges are elongated, and in some cases focal thickening of the granular layer and columns of parakeratosis are seen. All these features create a clinical appearance of a raised, papillary lesion. Occasionally, an increase in melanin in the basal cell layer is also evident. This correlates clinically with the tan or brown-colored lesions. Additionally, the lesional margins are sharply demarcated from the surrounding normal epithelium on microscopic examination.

Basal cell carcinoma (BCC), keratoacanthoma, and squamous cell carcinoma (SCC) have been reported to develop in cutaneous linear epidermal nevus, but this appears to be an extremely rare event. Ichikawa et al reported 16 cases of linear epidermal nevi associated with malignant change (BCC, SCC, Bowen’s disease, verrucous carcinoma, adnexal carcinoma). In some cases, exposure to physical agents (ultraviolet light and chemical carcinogens) was found to be a predisposing factor. Malignant change should be suspected when lesions exhibit sudden localized growth or ulceration. This low risk of malignancy is in contrast to nevus sebaceus, which is more frequently associated with the development of malignant tumors.

The differential diagnosis of ILVEN must be done with various dermatoses, such as other epidermal nevi, Darier’s disease, linear porokeratosis, linear lichen planus, linear psoriasis, and lichen striatus. Lichen striatus may mimic ILVEN clinically but is self limited. ILVEN can be distinguished because of its earlier onset and lack of spontaneous regression. Lesions are potentially premalignant with a 15–20% risk of malignant transformation, hence the early surgical removal of these lesions should be considered. Patients with extensive epidermal nevi and systemic abnormalities should be suspected of having the epidermal nevus syndrome. Evaluation and management of patients with epidermal nevus syndrome requires a multidisciplinary team approach involving the dermatologist, pediatrician, ophthalmologist, neurologist, plastic surgeon, and orthopedic services.

Many therapies have been attempted for the epidermal nevi including intralesional as well as topical steroids, topical and systemic retinoids, topical 5-fluorouracil, podophyllin, dermabrasion, cryosurgery, and excisional surgery. However, these treatment options tend to either fall short of complete eradication of the nevus or result in an unacceptable scar that can be as disfiguring as the nevus itself. Variable results with
laser treatment of epidermal nevi including Argon, Er: YAG, pulsed dye, and CO₂ laser have been demonstrated in the past. Recent developments in CO₂ laser technology have made the modern pulsed and scanned CO₂ laser as an excellent treatment of choice for the patients with epidermal nevi.²⁴

ILVEN is markedly refractory to therapy. There are reports of the use of many alternatives in the management of this condition: Topical glucocorticoids applied under occlusion, intralesional corticosteroids, combination of tretinoin 0.1% and fluorouracil 5%; anthralin, tar, vitamin D₃ analogues, surgical excision, cryotherapy with liquid nitrogen, and laser therapy with carbon dioxide. However, no research has shown consistent results about the superiority of any one of these therapies.⁶

A diagnosis of ILVEN syndrome should be considered in patients with extensive verrucous, pruritic epidermal nevi, and/or systemic abnormalities. A thorough mucocutaneous, neurologic, ophthalmic, and orthopedic examination is necessary with specific investigations depending on the involved system. A regular follow-up is necessary due to the risk of malignant transformation of the nevi and development of systemic manifestations.

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