Oral Linear Epidermal Nevus: A Review of the Literature and Report of Two New Cases

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Abstract Linear epidermal nevus (LEN) is a sporadic hamartomatous lesion of the skin due to the proliferation of clones of embryonic ectodermal cells, which are arranged according to a typical linear configuration known as Blaschko's lines. Oral involvement of LEN is very rare and few cases have been reported in the medical literature. We report two new cases of LEN with exclusive oral involvement, which presented with the typical unilateral or midline distribution. Oral LEN presents as an exophytic lesion with well defined borders and a verrucous or papillary surface which correspond, histologically, to epithelial papillomatosis with a moderate degree of hyperkeratosis and acanthosis. Oral LEN appears mainly at birth, grows slowly during childhood and stabilize by adolescence. Localized lesions do not show any recurrence after surgical removal but widespread lesions seem to have more risk of recurrence and are more difficult to manage. Functional problems and malignant transformation have not been reported.

Keywords Linear epidermal nevus · Hamartoma · Blaschko's lines · Epidermal nevus syndrome

Introduction

Linear epidermal nevus (LEN), also known as verrucous epidermal nevus or linear verrucous epidermal nevus, is an hamartoma included in the classification of epidermal nevi [1], a group of congenital malformations derived from embryonic ectoderm and characterized by the proliferation of the epithelium which is arranged in a typical linear configuration that follows Blaschko's lines [2, 3].

As ectoderm gives rise to keratinocytes and skin appendages, epidermal nevi are defined and classified according to the predominant cell type: predominance of keratinocytes (linear verrucous epidermal nevus), sebaceous glands (nevus sebaceous), pilosebaceous units (nevus comedonicus), sweat glands (apocrine and eccrine nevus) and mucosal epithelium (white sponge nevus). The term epidermal nevus syndrome refers to the association of any type of epidermal nevi with ocular, cardiovascular, neurological, cutaneous, skeletal and urological developmental abnormalities. Until now six distinct syndromes have been identified, each with a specific clinical, histopathological and genetic profile: Schimmelpenning syndrome, nevus comedonicus syndrome, pigmented hairy epidermal nevus syndrome, Proteus syndrome, congenital hemidysplasia-ichthyosiform dermatitis- limb defects syndrome and phacomatosis pigmentokeratotic. [4].

LEN is classified as localized when confined to one side of the skin and as diffuse when it shows either unilateral widespread (nevus unius lateris) or bilateral widespread (ichthyosis hystrix). LEN is mainly localized on the trunk with a circumferential orientation and on the limbs where shows a longitudinal orientation. Happle [2] has reported the typical linear configuration also on the head and neck area and found that oral mucosa involvement is extremely rare.

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Historically, since the first review of Brown and Gorlin [5], who reported 24 patients with oral and cutaneous LEN, only 11 patients with oral involvement have been described in the medical literature [6–9] and, among these, only three cases were reported with exclusive oral localization.

In this paper we describe two new cases of LEN with exclusive oral localization and review the pertinent literature regarding this rare entity.

Case Reports

Case 1. In October 2000, a 32-year-old male patient presented to our Reference Centre with multiple, gray coloured, papillary lesions involving the left lower lip and the adjacent homolateral vestibular mucosa (Fig. 1a). The lesions were longitudinally oriented and didn't cross the midline. He also presented, on the tongue, a diffuse, large papillary lesion extending from the middle to the anterior left margin (Fig. 1b). The patient, in good general health with the exception of a seborrheic dermatitis localized at the scalp, reported that around the age of twelve was hospitalized for a biopsy of “undefined lesions of the oral mucosa” and that, during the same period of time, a mandibular odontoma was removed. We were unable to obtain any clinical and/or histopathological documentation regarding this past event.

The lip lesions were biopsied and the histopathological examination revealed hyperkeratosis, acanthosis and papillomatosis (Fig. 2a, b). No further surgery or other treatments were performed. At the last follow-up (June 2009) the oral lesions were still present without any significant modifications regarding their previous size and distribution.

Case 2. In October 2007, a 4-year-old male child was referred to our observation after that the mother had noted a nodular lesion on the child's palate. The patient showed a pink coloured, sessile, large nodule, with a characteristic micro papillary surface, resembling a raspberry, located in the midline of the hard palate (Fig. 3). During clinical examination no cutaneous or dental lesions were detected. The child was in perfect health and did not present any symptoms or clinical signs which required at that time any further clinical systematic evaluation. The age of onset, the clinical aspect and the localization on the palatal midline made us to suspect LEN. The palatal nodule was totally removed and histopathological examination revealed hyperkeratosis, acanthosis and papillomatosis confirming the diagnosis of LEN (Fig. 4). At the last 2-year follow up (September 2009), the child was in perfect physical health and did not show any palatal recurrence or other clinical signs of disease.

Fig. 1 Case 1. **a** The patient presents multiple papillary lesions of the left lower lip that do not cross the midline; **b** Large papillary lesions are visible on the left border of the tongue. Note that lip and tongue lesions are located on the same side

Discussion

Oral involvement of LEN is a rare finding. The data collected in Table 1 from a Medline search of the English-speaking literature give rise to several considerations. First of all this condition does not show sex preference (male/female ratio: 7 vs. 6). The lesions mainly appear to develop at birth or during the first months of life and show a tendency to enlarge slowly during childhood, whilst they stabilize by adolescence [10]. Most cases of LEN appear to be sporadic, although some familial cases have been reported [11]. The anatomic distribution of the lesions appears quite characteristic with skin and oral lesions always occupying the same side of the body. On the skin

Fig. 2 Case 1. **a** Histopathological examination reveals multipapillary lesion with borders sharply demarcated from the normal surrounding epithelium. (H&E, original magnification $\times 2$); **b** Higher magnification shows intense epithelial hyperplasia, with parakeratosis and acanthosis. A mild inflammatory infiltrate is present in the underlying connective tissue. (H&E, original magnification $\times 4$)

Fig. 3 Case 2. Exophytic nodular lesion located in the midline of the hard palate

the nevus lesions are arranged according to a typical linear pattern known as Blaschko's lines. These particular lines, which were described in 1901 by the German dermatologist Alfred Blaschko [2], represent a pattern assumed by many different nevoid and acquired skin diseases on the human skin. Blaschko's lines do not correspond to any known nervous, vascular or lymphatic structures (also they differ from the system of dermatomes!). The embryological basis of the distribution pattern of these lines remains so far an enigma, although it has been reported that they may represent visible embryonic migration paths of clones of ectodermal cells that carry genetic disorders. As an alternative explanation it has been said that they may result

Fig. 4 Case 2. Histopathological examination shows a well defined papillary lesion with multiple epithelial projection and elongation of the rete ridges. (H&E, original magnification $\times 4$)

from an inborn error of morphogenesis due to a single mutant gene or stretching of the skin during embryogenesis [3, 12]. In Table 1 are listed seven mucocutaneous cases of LEN (case 4–9 and 13) with the skin and oral manifestations always with a linear configuration and homolateral distribution.

Of six cases of LEN with exclusive oral localization, three (case 2, 11 and 12) showed a characteristic palatal midline distribution and three (case 1, 3 and 10) occupied different anatomical zones of the mouth but always without crossing the oral midline. These topographical considerations may suggest that Blaschko's lines, originally described in the skin, may have an intraoral counterpart as result of the proliferation of oral clones of epithelial progenitor cells [13].

In Table 1 are also listed three patients (case 2, 11 and 12) in whom the lesions developed in the midline of the palate with the aspect of a well circumscribed, sessile nodule. This particular presentation has been described by Hickman [6] under the term of "verrucous nevus". In these cases the clinical aspect and the absence of a cutaneous counterpart makes difficult the differential diagnosis from other similar oral diseases, especially the human papillomavirus related lesions and among these squamous papilloma and verruca vulgaris. Squamous papilloma is observed during 30–60 years of age; at difference oral-LEN develops at birth or during childhood. In addition, squamous papilloma it is generally peduncolated whilst oral-LEN generally is sessile. At difference is also the colour with squamous papilloma showing a white surface being frequently keratinized while oral-LEN shows the same colour as the surrounding normal mucosa. Finally, squamous papilloma does not show tendency to recur after excision whilst oral LEN is more prone to recur during the period of the patient's somatic growth. Although, there are no apparent histological differences between oral LEN and squamous papilloma, the last one shows an epithelium with

Table 1 Clinical features of 13 patients with oral LEN

Author	Case no.	Sex	Side of body	Age of onset	Oral lesions	Skin lesions	Dental abnormalities
Present study	1	M	Left	Childhood	Left lower lip mucosa and left border of the tongue	None	Odontoma
Haberland Carrodeguas [9]	2	M	Midline	Childhood	Midline hard palate	None	None
	3	F	Left	4 years	Left buccal mucosa, retromolar pad, tuberosity, and palate-pharyngeal fold	None	None
	4	M	Right	Birth	Right soft palate and midline	Right nasolabial area and upper lip vermillion	None
	5	M	Left	Birth	Left buccal mucosa, maxillary Right soft palate and midline hard palate	Left arm, chest, neck and perioral mucosa	None
	6	M	Right	Birth	Right buccal mucosa, maxillary vestibule, hard and soft palate. Right side of dorsum of the tongue	Right upper lip vermillion and perioral skin	Enamel, hypoplasia, hypodontia
Ozcelik et al. [8]	7	F	Right	Birth	Midline soft and hard palate	Midline chin and right neck	None
	8	F	Right	Birth	Right labial commissure, buccal mucosa, soft and hard palate. Uvula enlargement	Right corner of the mouth and cheek	None
Coley-Smith et al. [7]	9	F	Left	Birth	Left buccal and palatal mucosa Uvula enlargement	Midline lower lip Left corner of the mouth and cheek	None
	10	M	Midline/ right	Birth	Midline dorsum of the tongue Right palatal mucosa and gingival	None	None
Hickman et al. [6]	11	F	Midline	Midline hard palate	None	None	
	12	M	Midline	Childhood	Midline soft and hard palate	None	None
	13	F	Left	3 years	Upper left gingiva Left lip commissure	Skin below the left eye	None

a higher degree of hyper-para/ortokeratosis and sometimes presence of koilocytes. Oral verruca vulgaris is observed mainly in children and may resemble oral LEN because of its clinical aspects. Verruca vulgaris is a sessile lesion of limited size showing a clear preference for the vermillion border, labial mucosa and anterior tongue. Verruca vulgaris enlarges rapidly during a short period of time then stabilizing to its maximum size (usually 4–5 mm), whereas LEN has the tendency to enlarge constantly during somatic growth stabilizing by adolescence. Histopathologically, verruca vulgaris is characterized by numerous papillary projections covered by hyperkeratotic stratified squamous epithelium with the typical “cupping” effect due to the elongated rete ridges that tends to converge toward the centre of the lesion.

When LEN is localized on the dorsal tongue or palate may resemble lymphangioma or, when observed in adults, may mimic verrucous carcinoma. In a recent article, Haberland-Carrodeguas et al. [9] reported five new cases of LEN of the oral mucosa that appeared as large, multiple,

coalescing pink papillary nodules, located in every part of the mouth including lips, buccal and vestibular mucosa, gingiva, tongue, soft and hard palate, maxilla tuberosity, palatopharyngeal fold and the retromolar pad. These Authors also observed that lesions always had an unilateral or a midline distribution. According to the published literature, cases of oral LEN may be associated with several odontogenic conditions such as odontoma, ameloblastoma, central giant cell granuloma and enamel hypoplasia [13–17]. Our patient N.1 had also an odontoma which was discovered at the age of 12 in coincidence with oral LEN.

The histopathological aspects of oral-LEN include papillomatous projections with a moderate degree of hyperkeratosis, acanthosis and elongation of the rete ridges; these features correspond to the clinical aspect of a raised papillary lesion with a micropapillary or verrucous surface. In addition, the well defined margins of the clinical lesions well correspond, on microscopic examination, to the sharply demarcated borders from the normal surrounding epithelium. In case 13 (see Table 1), Hickman [6] found

unusual small islands of non keratinized squamous epithelium in the underlying connective tissue, which were explained as presumable developmental epithelial inclusions. Some Authors [5, 6] have reported that a mild chronic inflammatory infiltrate can be present in the lamina propria.

Regarding a possible neoplastic transformation of LEN it is of interest to mention that basal and squamous cell carcinoma, verrucous carcinoma and adnexal carcinoma arising from cutaneous LEN have been reported but, to date, no cases of malignant transformation of oral LEN have been reported [18].

From a therapeutic point of view the rarity of LEN with oral involvement prevents from having any definitive treatment guidelines. Although, several treatment modalities have been reported for the cutaneous lesions, such as surgical excision, laser ablation, cryotherapy, dermabrasion, chemical peels, topical corticosteroids and systemic steroids, no information are available for oral lesions [19, 20]. In our Case 2 the surgical removal of the palatal nodule was not followed by recurrence, according to the outcomes of other Authors [6, 9]. Widespread oral lesions are more difficult to manage as they show the tendency to recur after surgery [6]. In cases of patients with extensive oral involvement no functional problems have been described. In our Case 1 the extensive oral lesions were present for about 20 years without causing functional problems.

Conclusions

Linear epidermal nevus (LEN) is a cutaneous hamartoma derived from the proliferation of embryonic ectodermal cells which are arranged according to a typical linear configuration pattern known as Blaschko's lines.

Oral LEN is an extremely rare disease, mainly present at birth, which can develop from any oral area as isolated or widespread lesions. The anatomic distribution of LEN shows some remarkable aspects such as the feature that cutaneous and oral LEN always occupy the same side of the body with a characteristic unilateral or midline distribution. These peculiar clinical features may suggest that cutaneous Blaschko's lines may have a mucosal counterpart.

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