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REVIEW ARTICLE

Review of linear epidermal nevus with oral mucosal involvement – series of five new cases

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INTRODUCTION: Linear epidermal nevi are sporadic hamartomatous alterations of the epidermis and superficial dermis that clinically appear as verrucous papules and plaques distributed in a linear pattern following Blaschko's lines. Their extent varies from unilateral involvement (nevus unius lateris) to extensive bilateral involvement (ichthyosis hystrix). Oral mucosal lesions have rarely been described.

AIMS: We review the literature, focusing on the rare intraoral manifestations of linear epidermal nevus.

CASE SERIES: We present a series of five new cases with oral mucosal involvement. Four cases had associated cutaneous lesions and one case had oral lesions exclusively. Histopathologic evaluation of lesional tissue in four cases showed hyperkeratosis, acanthosis, epithelial hyperplasia, and papillomatosis. Dental abnormalities, consisting of enamel hypoplasia and congenitally missing teeth, were noted in one patient adjacent to the oral lesions.

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Keywords: linear epidermal nevus; epidermal nevus syndromes; cutaneous; benign epithelial disorders; oral mucosa

Introduction

Epidermal nevi are defined as congenital malformations or hamartomas derived from embryonic ectoderm. This ectoderm gives rise not only to keratinocytes but also to skin appendages. Therefore, epidermal nevi can be further classified into variants according to the predominant epidermal structure involved. Additionally, they are also classified according to their clinical appearance, distribution, and extent of involvement (Rogers *et al*, 1989; Rogers, 1992). Lesions are usually noted at birth or infancy and are usually non-familial (Naylor, 1996).

Linear epidermal nevus (LEN), also known as verrucous epidermal nevus or linear verrucous epidermal nevus, presents clinically as tan or brown verrucous papules, arranged in a linear configuration following skin tension lines (Blaschko's lines) and composed primarily of surface epithelium (Fitzpatrick *et al*, 1999). It is not known why the lesions follow this skin pattern, but it probably represents the migration paths of embryonic cells. Many inherited and acquired diseases of the skin or mucosa manifest themselves according to these patterns, creating the visual appearance of stripes. Examples of these conditions include nevus sebaceus, inflammatory linear verrucous nevus, incontinentia pigmenti, lichen striatus, linear lichen planus, and linear lupus erythematosus (Bolognia *et al*, 1994).

The prevalence of LEN is estimated to be 1:1000 live births (Solomon and Esterly, 1975). The lesion can enlarge slowly during childhood but by adolescence the process tends to stabilize and does not extend any further (Naylor, 1996). Based on the extent of the lesions, they are classified as either localized or diffuse (systematized). Localized lesions that are confined to one side of the body are often referred to as nevus unius lateris, whereas extensive bilateral lesions are referred to as ichthyosis hystrix (Lever and Schaumburg-Lever, 1990). LEN are found at any cutaneous site, but tend to occur along the long axis of an extremity or across the trunk. Other epidermal nevus variants distinguished by the epidermal structure involved include nevus sebaceus, nevus comedonicus, eccrine nevus, Becker's nevus, and white sponge nevus (Naylor, 1996).

Epidermal nevus syndrome (ENS) also referred to as linear sebaceus nevus syndrome, Feuerstein-Mims syndrome, Schimmelpenning-Feuerstein syndrome or Solomon syndrome, is associated with epidermal nevus, in addition to central nervous system (CNS) abnormalities such as mental deficiency and seizures, skeletal defects,

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ocular defects and other anomalies (Solomon *et al*, 1968; Gorlin *et al*, 2001). Currently, the concept of a single ENS with various clinical variants has been challenged. There is evidence that six distinct ENS exist, which can be distinguished by clinical, histopathologic and genetic criteria. These entities include Schimmelpennig syndrome (Sebaceus nevus syndrome), nevus comedonicus syndrome, pigmented hairy ENS (Becker nevus syndrome), Proteus syndrome, phakomatosis pigmentokeratotika and congenital hemidysplasia with ichthyosis form nevus and limb defects syndrome (Happle, 1995; Vidaurri-de la Cruz *et al*, 2004).

Brown and Gorlin (1960) reported a case of LEN with oral involvement and reviewed the worldwide literature for additional reports. They found that the oldest known report of oral involvement associated with this entity dates back to 1865 (Church, 1865). Their review analyzed a total of 24 cases of LEN with oral mucosal involvement. Hickman *et al* (1988) reported three cases of linear epidermal nevi with oral lesions, two of which presented with oral lesions exclusively. Coley-Smith and Shaw (1996) described two more examples in the literature. The most recent article is by Özçelik *et al* (2005) who reported a case with both facial and intraoral lesions.

We present five new cases of LEN with oral mucosal involvement (Table 1). These patients did not present with CNS, ocular, skeletal, or any other abnormalities. All lesions had been present at birth or for as long as the patient could remember. Four cases had associated cutaneous lesions and one case had oral lesions exclusively. Histopathologic sections of lesional tissue were reviewed for four of the five cases.

Description of cases

Case 1

A 13-year-old Caucasian female patient presented with light brown papules that had a verrucous surface, and a linear pattern of distribution. These lesions were located on the midline of the chin and extended to the right neck (Figure 1). Intraorally, she had one large nodule with a pink, papillary surface that was located on the midline of the hard and soft palate area (Figure 2). Because of the characteristic clinical appearance of the oral and cutaneous lesions and their midline location the lesions were diagnosed clinically as LEN and were not biopsied.

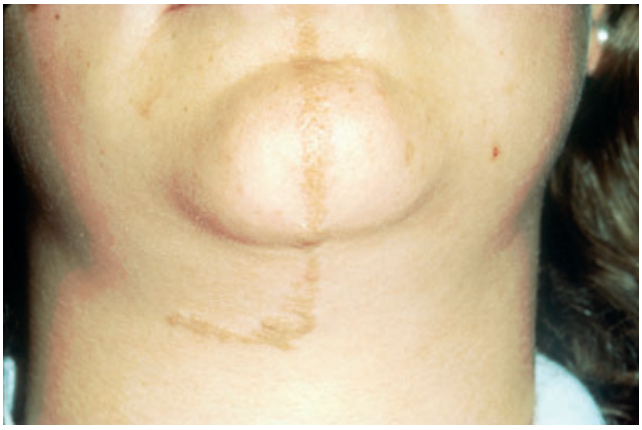

Figure 1 Skin lesions of patient 1 at initial visit. Note the linear and midline distribution

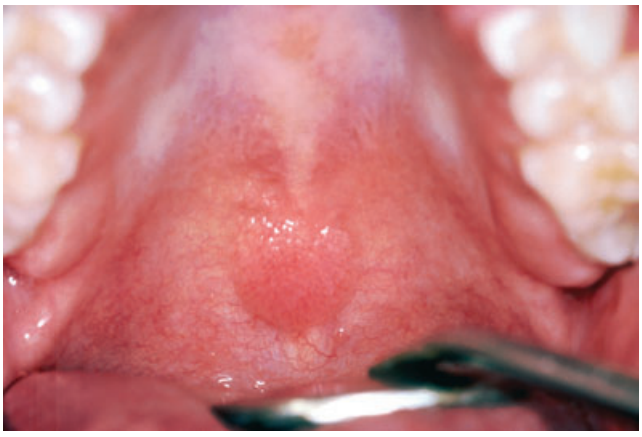

Figure 2 Intraoral lesion in patient 1. Large papillary lesion located in the midline of the junction of the hard and soft palate

This patient was re-evaluated 4 years after the initial visit and, at that time, the only change noted was a slight increase in size of the cutaneous lesions (Figure 3). The patient was not interested in having the cutaneous lesions surgically removed.

Case 2

A 17-year-old Hispanic male patient presented with multiple coalescing pink papillary oral lesions that extensively involved the right buccal mucosa, the right

Table 1 Clinical features of five patients with oral mucosal linear epidermal nevus

Case no.	*Sex*	*Side of body*	*Age of onset*	*Oral lesions*	*Skin lesions*	*Dental abnormalities*
1	F	Right	Birth	Midline hard and soft palate	Chin and neck	None
2	M	Right	Birth	Buccal mucosa, maxillary vestibule, hard and soft palate	Upper lip vermilion and perioral skin	Enamel hypoplasia and hypodontia
3	M	Left	Birth	Buccal mucosa, maxillary vestibule, and attached gingiva	Arm, chest, neck, and perioral skin	None
4	M	Right	Birth	Soft palate and midline hard palate	Nasolabial area and upper lip vermilion	None
5	F	Left	4 years	Buccal mucosa, retromolar pad, tuberosity, and palatopharyngeal fold	No skin lesions	None

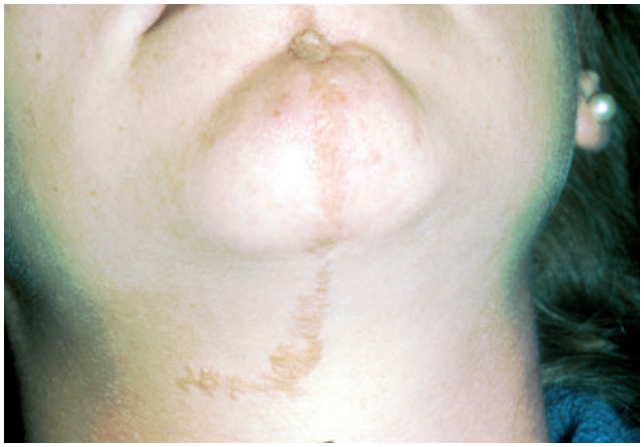

Figure 3 Patient 1 presents for evaluation 4 years after her initial pictures were taken. Lesions have slightly increased in size

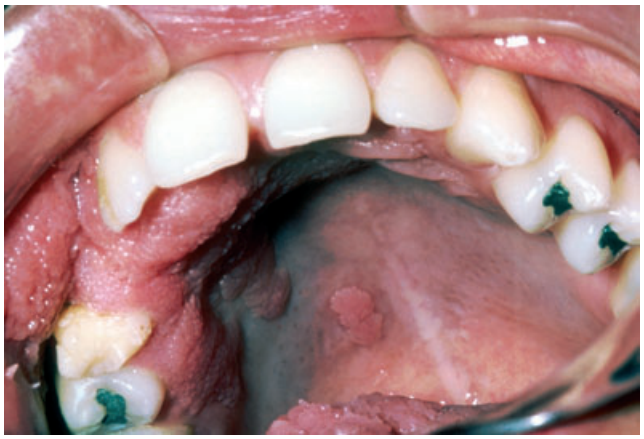

Figure 4 Patient 2 presents with extensive papillary and verrucous lesions of the right labial mucosa, gingiva, and hard palate

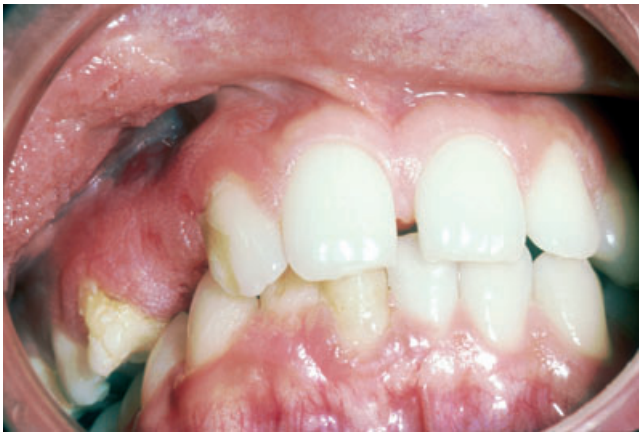

Figure 5 Patient 2 presents with mucosal lesions of LEN, as well as dental abnormalities. Patient has enamel hypoplasia on right maxillary first premolar and lateral incisor (teeth 5 and 7) as well as congenitally missing right maxillary canine (tooth 6)

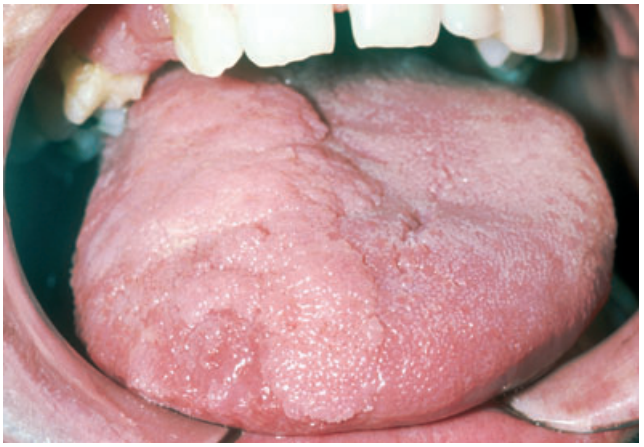

Figure 6 Patient 2 presents with extensive papillary lesions on the right-hand side of his tongue, resulting in unilateral macroglosia

maxillary vestibule, the right maxillary facial and palatal gingiva, as well as the right hard and soft palate (Figure 4). The maxillary right first premolar (tooth 5) and the lateral incisor (tooth 7) showed enamel hypoplasia while the canine on the affected side (tooth 6) was congenitally missing (Figure 5). He also presented with a diffuse sessile papillary lesion extending from the base to the anterior dorsal portion of the tongue on the right-hand side (Figure 6). Representative intraoral lesions were biopsied, showing papillomatosis, acanthosis, and moderate hyperkeratosis. Facial skin examination showed two light-brown papillary papules located on the right vermilion border of the upper lip, extending toward the perioral skin (Figure 7). No further treatment was rendered for this patient.

Case 3

A 6-year-old Caucasian male presented with extensive papillary skin lesions on the left-hand side of his body. These lesions were distributed in a linear pattern and located on the neck area, chest, arm, and perioral skin (Figures 8 and 9). According to the patient's parents,

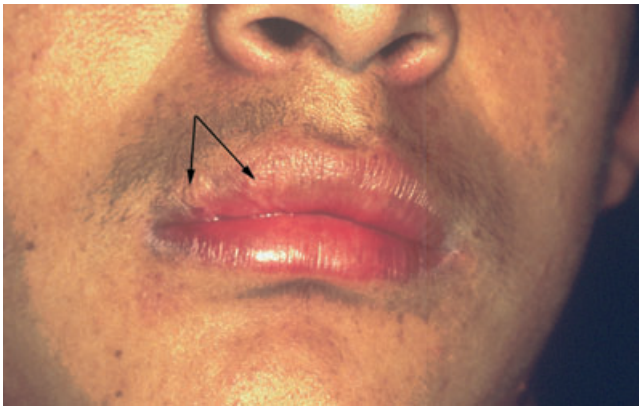

Figure 7 Extraoral skin lesion noted on patient 2. Arrows point to small papillary lesions on the right vermilion and perioral skin

the lesions were noted at birth and gradually changed from skin-colored to light-brown color over a period of years. The child also had intraoral lesions consisting of

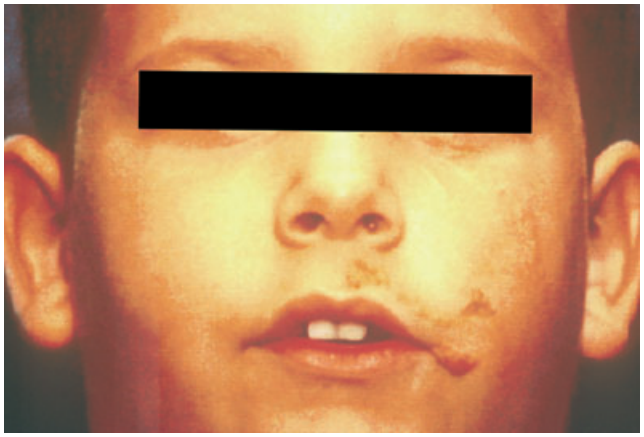

Figure 8 Patient 3 shows extensive tan and brown papillary lesions on the left perioral skin and cheek

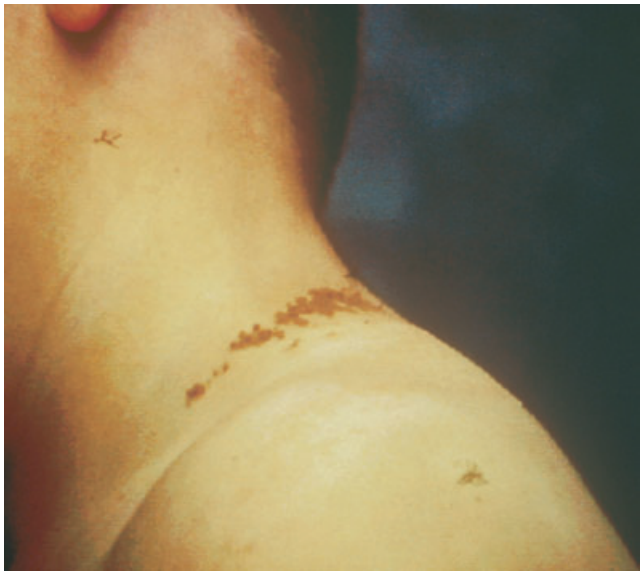

Figure 9 Patient 3 with extensive papillary brown papillary lesions on the left-hand side of the neck

papillary nodules on the left buccal mucosa, vestibule, and attached gingiva. No tooth abnormalities were noted. Biopsies of the facial and oral lesions showed epithelial hyperplasia, papillomatosis, and hyperkeratosis. The oral lesions were completely excised and have not recurred.

Case 4

A 63-year-old Caucasian male patient presented with skin and oral lesions that had been present since childhood. Multiple verrucous papules were noted on the skin of the right nasolabial area and the vermilion border of the upper lip (Figure 10). Intraorally, multiple papillary nodules were noted on the right anterior soft palate and midline hard palate (Figure 11). Biopsies from the vermilion and palatal lesions demonstrated papillomatosis, hyperkeratosis, acanthosis, and a sharp demarcation from the adjacent normal mucosa

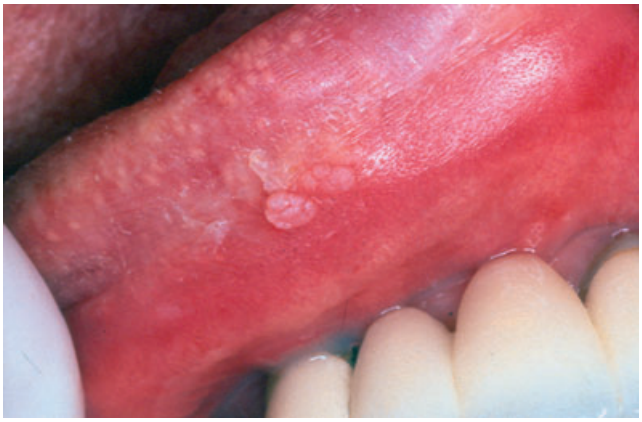

Figure 10 Patient 4 with multiple papillary lesions on the right vermilion and labial mucosa

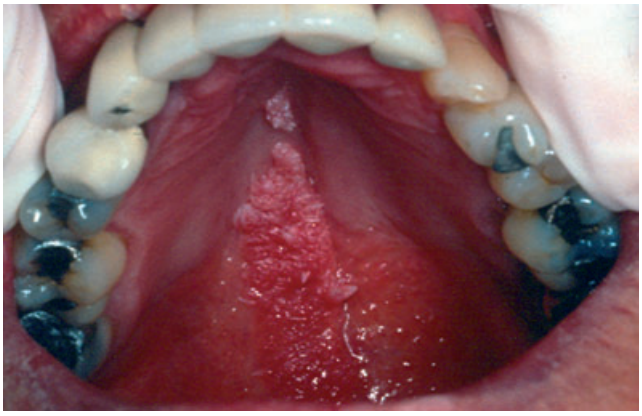

Figure 11 Patient 4 with extensive pink, papillary lesions on the right-hand side and midline of the hard and soft palate

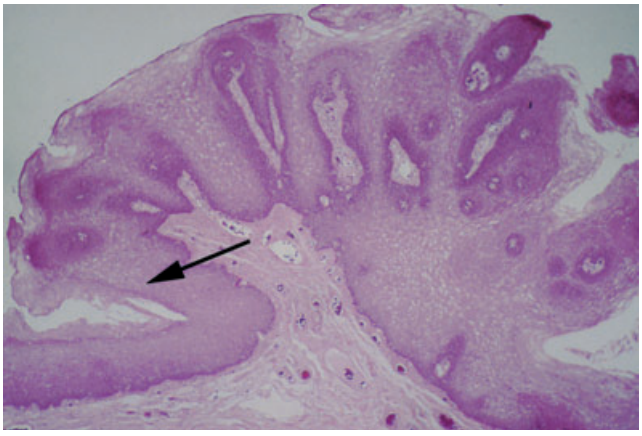

Figure 12 Histological section of soft palate lesion showing acanthosis, parakeratosis, papillomatosis, and a sharp demarcation from the normal tissue (arrow)

(Figure 12). No recurrence of the excised lesions were reported during a 5-year follow-up.

Case 5

A 4-year-old Caucasian female patient presented with white multifocal papillary verrucous papules and

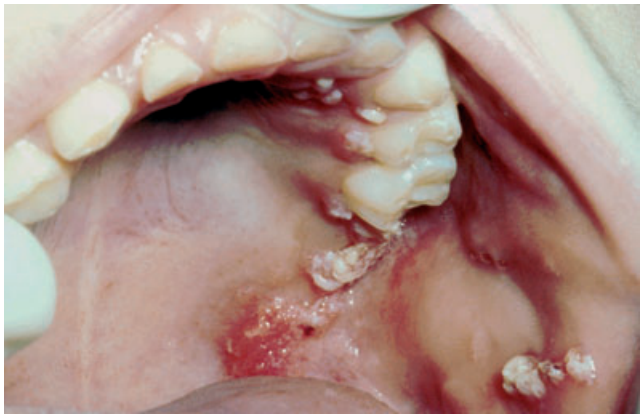

Figure 13 Patient 5 with multiple, white, papillary lesions on the left buccal mucosa and retromolar pad

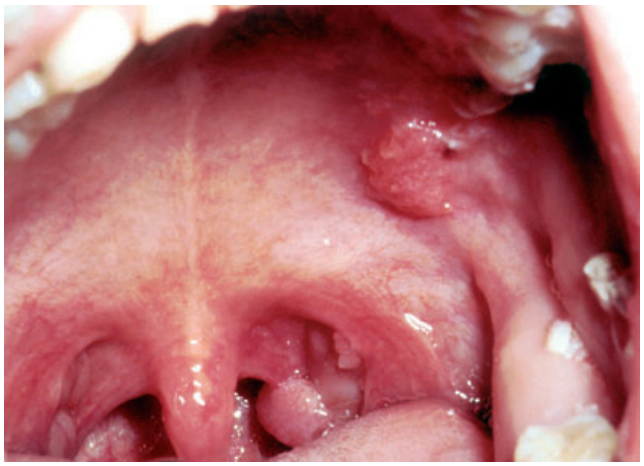

Figure 14 Patient 5 with large papillary lesions on the left soft palate and palatopharyngeal fold

nodules on the left buccal mucosa, retromolar pad, palate, tuberosity, and palatopharyngeal fold (Figures 13 and 14). Representative lesions were biopsied and the microscopic features consisted of hyperparakeratosis, hypercellularity, and papillomatosis. No dental abnormalities or skin lesions were noted on this patient.

Discussion

Oral involvement of LEN 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, hard and soft palate and gingiva. The clinical differential diagnoses for these rare intraoral lesions include human papillomavirus-related lesions (squamous papillomas, verruca vulgaris, condyloma, focal epithelial hyperplasia), lymphangioma for tongue and palatal lesions, and even verrucous carcinoma for lesions that are observed in adults. In a review of 24 cases, Brown and Gorlin (1960) 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. 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 cases occurred slightly more often on the right-hand side (3:2) but the clinical appearance and intraoral locations were similar. In addition, one of the five cases (20%) also presented with dental abnormalities which included enamel hypoplasia and hypodontia, which is a percentage similar to that reported by Brown and Gorlin (1960).

The diagnosis of LEN exclusively in the oral cavity is a distinct rarity. Only one of the patients in the present study had oral lesions without concurrent cutaneous involvement. Although the lesions had a unilateral distribution, multiple oral mucosal sites were involved, tracking from the buccal mucosa to the palatopharyngeal fold. Similarly, Hickman *et al* (1988) reported two cases with exclusive oral lesions, although these patients had lesions only in the midline hard palate. These authors considered this a distinct process and proposed the term 'verrucous nevus'; however, this new terminology is confusing and not widely accepted.

The patients reported in this series had no associated CNS, skeletal, or ocular abnormalities and thus did not fulfill the criteria for the diagnosis of ENS. In contrast to LEN, however, there have been numerous reports of oral lesions in patients diagnosed with this syndrome (Kelley *et al*, 1972; Dunbar *et al*, 1985). In addition to oral mucosal lesions, a variety of skeletal lesions and dental abnormalities have been described, including: giant cell granuloma (Kaplan *et al*, 1993), facial hemihypertrophy (Muller *et al*, 1980), ameloblastoma (Basopoulou-Kyrkanidou *et al*, 2000), compound odontomas (Baghaei-Rad *et al*, 1982), regional odontodysplasia (Slootweg and Meuwissen, 1985), and enamel hypoplasia (Kelley *et al*, 1972).

The histopathologic features of epidermal nevi are described as hyperkeratosis, acanthosis, and papillomatosis. There is usually a moderate degree of hyperkeratosis and acanthosis. The rete ridges are elongated, and in some cases focal thickening of the granular layer and columns of parakeratosis are seen (Brown and Gorlin, 1960; Hickman *et al*, 1988; Fitzpatrick *et al*, 1999). All these features create a clinical appearance of a raised, papillary lesion. Occasionally, an increase in melanin in the basal cell layer is 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 (Su, 1982; Lever and Schaumburg-Lever, 1990). This finding is consistent with the clinical presentation of well-delineated papules and nodules with clearly defined borders.

Basal cell carcinoma (BCC) (Horn *et al*, 1981), keratoacanthoma (Braunstein *et al*, 1982; Rosen, 1982), and squamous cell carcinoma (SCC) (Cramer *et al*, 1981) have been reported to develop in cutaneous LEN, but this appears to be an extremely rare event. In a recent review, Ichikawa *et al* (1996) 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 (UV 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 (Jones and Heyl, 1970; Rinaggio *et al*, 2002). To date there have been no reports of oral lesions of LEN that have undergone malignant transformation.

Treatment of cutaneous lesions of LEN consists of surgical excision, extending into the deep dermis to avoid recurrence. Surgical excision may not be possible in certain cases of extensive involvement. In these cases other treatment modalities have been used, including laser ablation (Michel *et al*, 2001), cryotherapy, dermabrasion, and chemical peels with trichloroacetic acid or phenol (Fox and Lapins, 1983). Recurrence is common with these treatments as they remove only the superficial portions of the lesion. Alternatively topical treatment with podophylin, retinoic acid, anthralin, alpha-hydroxy acids, intralesional corticosteroids, and topical corticosteroids has been relatively ineffective (Fox and Lapins, 1983). There are at least two reports describing the effectiveness of combination therapy with 5-fluorouracil (5-FU) and topical tretinoin (Retin-A) in the management of cutaneous linear epidermal nevi (Nelson *et al*, 1994; Kim *et al*, 2000). Although too few oral LEN cases have been described to predict the treatment outcome, Hickman *et al* (1988) did report a recurrence after partial removal of an oral lesion of LEN. At the time of submission of this report, none of our cases had recurrence after biopsy or excision of lesions.

References

Baghaei-Rad M, Doku C, Ficarelli J (1982). Epidermal nevus syndrome with maxillary involvement. *J Oral Maxillofac Surg* **40:** 821–823.

Basopoulou-Kyrkanidou E, Alexanridis C, Tosious KI *et al* (2000). Epidermal nevus syndrome with development of a mandibular ameloblastoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **90:** 64–70.

Bolognia JL, Orlow SJ, Glick SA (1994). Lines of Blaschko. *J Am Acad Dermatol* **31:** 157–190.

Braunstein BL, Mackel SE, Cooper PH (1982). Keratoacanthoma arising in a linear epidermal nevus. *Arch Dermatol* **118:** 362–363.

Brown HM, Gorlin RJ (1960). Oral mucosal involvement in nevus unius lateris (ichthyosis hystrix). *Arch Dermatol* **81:** 61–67.

Church W (1865). Report of a case of ichthyosis with congenital malformation of the aorta. *St Barth Hosp Rep* **1:** 198–200.

Coley-Smith A, Shaw L (1996). Oral findings in patients with epidermal neavi: a report of two cases. *Dent Update* **23:** 158–160.

Cramer SF, Mandel MA, Hauler R *et al* (1981). Squamous cell carcinoma arising in a linear epidermal nevus. *Arch Dermatol* **117:** 222–224.

Dunbar SY, Fantasia JE, Miller A (1985). Epidermal Nevus syndrome: report of a case with oral involvement. *J Pedod* **9:** 169–174.

Fitzpatrick TB, Eisen AZ, Wolff K *et al* (1999). Epidermal nevus. In: Fitzpatrick TB, Eisen AZ, Wolff K, eds. *Dermatology in general medicine*, Vol. 1, 5th edn. McGraw Hill, Inc: New York, NY, pp. 876–878.

Fox BJ, Lapins NA (1983). Comparison of treatment modalities for epidermal nevus: a case report and review. *J Dermatol Surg Oncol* **9:** 879–885.

Gorlin RJ, Cohen MM, Hennekam RCM, eds (2001). Schimmelpenning syndrome (formerly epidermal nevus syndromes). In: *Syndromes of the head and neck*, 4th edn. Oxford University Press: New York, NY, pp. 484–485.

Happle R (1995). Epidermal nevus syndromes. *Semin Dermatol* **14:** 111–121.

Hickman RE, Eveson JW, Cawson RA (1988). Nevus unius lateris and intraoral verrucous nevi. *Oral Surg Oral Med Oral Pathol* **66:** 226–229.

Horn MS, Sausker WF, Pierson DL (1981). Basal cell epithelioma arising in a linear epidermal nevus. *Arch Dermatol* **117:** 247.

Ichikawa T, Saiki M, Kaneko M *et al* (1996). Squamous cell carcinoma arising in a verrucous epidermal nevus. *Dermatology* **193:** 135–138.

Jones EW, Heyl T (1970). Nevus sebaceous. A report of 140 cases with special regard to the development of secondary malignant tumors. *Br J Dermatol* **82:** 99–117.

Kaplan I, Metzker A, Calderon S (1993). Epidermal nevus syndrome with maxillary involvement. *Int J Oral Maxillofac Surg* **22:** 298–300.

Kelley JE, Hibbard ED, Giansanti JS (1972). Epidermal nevus syndrome. report of a case with unusual oral manifestations. *Oral Surg Oral Med Oral Pathol* **34:** 774–780.

Kim JJ, Chang MW, Shwayder T (2000). Topical tretinoin and 5-fluorouracil in the treatment of linear verrucous epidermal nevus. *J Am Acad Dermatol* **43:** 129–131.

Lever WF, Schaumburg-Lever G, eds (1990). Linear epidermal nevus. In: *Histopathology of the skin*, 7th edn. J.B. Lippincott: Philadelphia, PA, pp. 524–525.

Michel JL, Has C, Has V (2001). Resurfacing CO_2 laser treatment of linear verrucous epidermal nevus. *Eur J Dermatol* **11:** 436–439.

Muller JT, Pickett AB, Frederick FD (1980). Facial hemihypertrophy associated with nevus unius lateris syndrome. *Oral Surg Oral Med Oral Pathol* **50:** 226–228.

Naylor MF (1996). Benign epithelial tumors and hamartomas. In: Sams WM, Lynch PJ eds. *Principles and practice of dermatology*, 2nd edn. Churchill Livingstone: New York, NY, pp. 215–216.

Nelson BR, Kolansky G, Gillard M *et al* (1994). Management of linear verrucous epidermal nevus with topical 5-fluorouracil and tretinoin. *J Am Acad Dermatol* **30:** 287–288.

Özçelik D, Haydar Parlak A, Öztürk A *et al* (2005). Unilateral linear verrucous epidermal nevus of the face and oral mucosa. *Plast Reconstr Surg* **115:** 17e–19e.

Rinaggio J, McGuff HS, Otto R *et al* (2002). Postauricular sebaceous carcinoma arising in association with nevus sebaceous. *Head Neck* **24:** 212–216.

Rogers M (1992). Epidermal nevi and the epidermal nevus syndromes: a review of 233 cases. *Pediatr Dermatol* **9:** 342–344.

Rogers M, McCrossin I, Commens C (1989). Epidermal nevi and the epidermal nevus syndrome – a review of 131 cases. *J Am Acad Dermatol* **20:** 476–488.

Rosen T (1982). Keratoachanthomas arising within a linear epidermal nevus. *J Dermatol Surg Oncol* **8:** 878–880.

Slootweg PJ, Meuwissen PRM (1985). Regional odontodysplasia in epidermal nevus syndrome. *J Oral Pathol* **14:** 256–262.

Solomon LM, Esterly NB (1975). Epidermal nevi and other congenital organoid nevi. *Curr Probl Pediatr* **6:** 3–15.

Solomon LM, Fretzin DF, Dewald RL (1968). The epidermal nevus syndrome. *Arch Dermatol* **97:** 273–285.

Su WPD (1982). Histopathologic varieties of epidermal nevus. *Am J Dermatopathol* **4:** 161–170.

Vidaurri-de la Cruz H, Tamayo-Sánchez L, Durán-McKinster C *et al* (2004). Epidermal nevus syndromes: clinical findings in 35 patients. *Pediatr Dermatol* **21:** 432–439.