



ORAL SURGERY

ORAL MEDICINE

ORAL PATHOLOGY

## ORAL AND MAXILLOFACIAL PATHOLOGY

Editor: Alan R. Gould

### Epidermal nevus syndrome with development of a mandibular ameloblastoma

Euterpe Bazopoulou-Kyrkanidou, DDS, MD, MS, Dr Dent,<sup>a</sup> Constantin Alexandridis, DDS, MS, Dr Dent,<sup>b</sup> Konstantinos I. Tosios, DDS, Dr Dent,<sup>c</sup> Stela Sotiriadou, DDS, Dr Dent,<sup>d</sup> and Angelos P. Angelopoulos, DDS, PhD,<sup>e</sup> Athens, Greece  
UNIVERSITY OF ATHENS

Epidermal nevus syndrome (ENS) is a hamartoneoplastic syndrome characterized by the association of epidermal nevi with abnormalities in other organ systems. We report a 32-year-old woman with ENS that, in addition to cutaneous manifestations, showed red plaques on the maxillary and mandibular labial alveolar mucosa and a papillomatous lesion of the midline posterior hard palate. Radiographic examination of the jaws was noncontributory. Approximately 5 years later, a follicular ameloblastoma developed in the mandible. The tumor showed duct-like cystic spaces, continuity with the overlying epithelium, and globular myxomatous areas in the connective tissue. The palatal lesion was diagnosed as papilloma, whereas the maxillary plaques showed nonspecific mucositis. The association of ameloblastoma with ENS is discussed. This is the second case of ENS associated with ameloblastoma reported in the medical literature. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;90:64-70)

Epidermal nevus syndrome (ENS) is a hamartoneoplastic syndrome<sup>1</sup> characterized by the association of epidermal nevi with abnormalities in other organ systems.<sup>1-4</sup> The central nervous system, skeletal system, and eyes are most commonly involved.<sup>1,3,4</sup> Cardio-vascular and genitourinary anomalies, oral lesions, skin lesions other than epidermal nevi, and neoplasms may also occur.<sup>3,4</sup> Multiorgan involvement is more commonly seen when epidermal nevi are widespread.<sup>3,5</sup>

The wide variety of signs by which ENS manifests may be explained by the assumption that ENS has a wide phenotypic variability<sup>3,6,7</sup> or that it encompasses a heterogeneous group of disorders (ENS syndromes) with common manifestations.<sup>2,4,8-10</sup> The designation

*epidermal nevus syndrome* has been used for lesions that have also been called by several other terms and eponyms.<sup>1,2,5,7,11</sup>

ENS is probably caused by the action of a lethal dominant mutation surviving by mosaicism.<sup>12</sup> Inheritance has not been proven because the majority of cases are sporadic.<sup>4</sup>

We report on a patient with epidermal nevus syndrome with cutaneous and oral manifestations that eventually developed an unusual mandibular ameloblastoma, and we discuss the histogenesis of the tumor and its association with ENS. This is the second case of ENS associated with ameloblastoma reported in the literature.

#### CASE REPORT

A 32-year-old woman was referred to the Department of Oral Pathology and Surgery, School of Dentistry, University of Athens, for "unusual gingival lesions."

#### History

The patient was born to apparently healthy, nonrelated parents (mother, 30 years old; father, 32 years old). Pregnancy and delivery were uneventful. Soon after birth, she was found to have several cutaneous and oral mucosal lesions, that is, linear papillomatous tumors of normal skin color in the midline of her upper and lower lip; small, linear, verrucous, pigmented tumors on the neck; papillomatous lesions of normal mucosal color covering the hard palate and the infe-

<sup>a</sup>Professor, Department of Oral Pathology and Surgery, Faculty of Dentistry.

<sup>b</sup>Associate Professor, Department of Oral Pathology and Surgery, Faculty of Dentistry.

<sup>c</sup>Clinical and Research Associate, Department of Oral Pathology and Surgery, Faculty of Dentistry.

<sup>d</sup>Assistant Professor, Department of Oral Pathology and Surgery, Faculty of Dentistry.

<sup>e</sup>Professor and Chairman, Department of Oral Pathology and Surgery, Faculty of Dentistry.

Received for publication June 21, 1999; returned for revision Sep 9, 1999; accepted for publication Jan 25, 2000.

Copyright © 2000 by Mosby, Inc.

1079-2104/2000/\$12.00 + 0 7/14/106301

doi:10.1067/moe.2000.106301



Fig 1. Skin scars on midline of upper and lower lip.

rior surface of the tongue; and small, red plaques on the alveolar mucosa. Her physical and mental development were regular, and no serious health problems were recorded. Her 26-year-old brother and 6-year-old daughter were healthy. No other member of the paternal or maternal families was reported to have such lesions. When she was 6 years old, the cutaneous, palatal, and lingual lesions were surgically removed; those of the alveolar mucosa were excised when she was 23 years. The palatal and alveolar lesions recurred.

### Physical examination

On admission (March 1992), the patient was found to have cutaneous scars on the midline of the upper and lower lip (Fig 1) and the right side of the neck (Fig 2). In addition, 4 small, skin-colored linear papules were noted above the sternal notch (Fig 2), as well as many freckles all over her body and a brown nevus above the pubes. Intraorally, there were 3 red plaques on the labial alveolar mucosa around the frenum of the upper lip, the left maxillary lateral incisor and canine, and between the mandibular lateral incisor and canine (Fig 3). The latter 2 plaques were adjacent to fixed prosthetic restorations. On the midline of the posterior hard palate there was a papillomatous tumor of normal color.

Panoramic and periapical radiographs showed marginal loss of the alveolar bone at both sides of the mandibular lateral incisor. This bone loss was attributed to the chronic local irritation caused by the gaping margins of the artificial tooth crown and the resulting dental plaque accumulation. Lateral and frontal skull radiographs were noncontributory.

The diagnosis of epidermal nevus syndrome was made, and surgical excision of oral and skin lesions was recommended.

The patient came back approximately 5 years later (May 1997) for evaluation of a mandibular enlargement, brought to her attention 8 to 9 months earlier. Oral examination showed an intraosseous tumor protruding to the lingual side of the mandible, along the area of the left central incisor and second premolar teeth (Fig 4). The labial side of the tumor was covered by a reddish, papillomatous plaque. The teeth of the involved area were mobile. The palatal tumor (Fig 5) and maxillary gingival lesions seen on initial presentation were unchanged. The rest of the oral mucosa and the dentition were normal, except for generalized gingivitis.



Fig 2. Skin scar on right side of neck and 4 linear nodules above sternal notch (arrows).

Panoramic radiograph (Fig 6) and a computed tomographic scan showed a large and irregular radiolucent lesion occupying the mandibular bone from the right canine to the left second premolar. The roots of the involved teeth were partly resorbed. Neurological, ocular, and skeletal abnormalities were not found, and laboratory investigation showed normal results.

Microscopic features of an incisional biopsy were interpreted as combined epithelial odontogenic tumor, primarily ameloblastoma, intermixed with areas of adenomatoid odontogenic tumor.

The tumor was totally resected by peripheral osteotomy, extending from the right lateral incisor to the left second premolar. The palatal and alveolar lesions were also surgically removed. The specimens were fixed in 10% buffered formalin, routinely processed, paraffin embedded, and stained with hematoxylin-eosin. The bone specimen was decalcified in an aqueous solution of 45% formic acid and 20% sodium citrate.

### Pathologic examination

#### *Mandibular tumor*

The specimen was occupied by a solid tumor of gray-white color and elastic consistency, measuring approximately 3 cm in diameter. Microscopic examination showed neoplastic epithelial cells arranged in nests or anastomosing trabeculae and cords in a fibrous connective tissue stroma. The epithelial islands consisted of loosely arranged reticulum-like or acanthomatous cells and showed a peripheral row of palisading cuboidal or columnar cells with reverse nuclear polarity and cytoplasmic vacuolization (Fig 7). Mitotic figures were scarce. Many tumor nests showed cystic spaces, occasionally surrounded by a single layer of low columnar or cuboidal cells, in a duct-like arrangement. A hyalin-like or amphophilic material was seen in some cystic spaces, as well as among the neoplastic cells. The inter-



Fig 3. Red plaques on labial alveolar mucosa.



Fig 4. Mandibular tumor protruding lingually, along area of left central incisor and second premolar teeth (arrows).



Fig 5. Papillomatous tumor on midline of posterior hard palate.

vening connective tissue was dense, fibrous, or myxoid, with focal lymphoplasmacytic infiltration and interstitial hemorrhage. Globular myxomatous areas in proximity to the neoplastic epithelium were also noticed (Fig 8).

The tumor was covered by papillary projections of parakeratinized epithelium, showing spongiosis, exocytosis, exoserosis, and elongated rete ridges that fused with the tumor islands in many areas (Fig 9). The distal border of the surgical specimen was infiltrated by neoplastic islands. Pathologic findings were consistent with infiltrative follicular ameloblastoma.

#### Palatal lesion

The palatal lesion measured 1×1×0.5 cm. Microscopically, it showed multiple papillary projections of parakeratinized squamous epithelium supported by stalks of mildly inflamed vascular connective tissue. The histopathologic diagnosis was papilloma.

#### Gingival lesions

The lesions of the upper alveolar mucosa totaled 1×0.4×0.2 cm. They consisted of parakeratinized epithelium with alternating areas of acanthosis and pseudoepitheliomatous hyperplasia, or atrophy and spongiosis with exocytosis, exoserosis, and microabscesses formation (Fig 10). The rete ridges were

elongated, broad, and anastomosing. The connective tissue was vascular and densely infiltrated by inflammatory cells, mainly lymphocytes, plasmacytes, and histiocytes. The histopathologic diagnosis was nonspecific mucositis.

#### Follow-up

Three months after the surgical excision, the palatal tumor and gingival lesions recurred. The palatal tumor was re-excised and, in addition to histopathologic features of the primary lesion, it showed acanthosis and hyperplasia of the basal cell layer.

#### DISCUSSION

Our patient had, in addition to the history of congenital nevi in the midline of the face and neck, cutaneous nevi in the midline of the neck and oral lesions consistent with ENS. Epidermal nevi may occur as isolated, sporadic lesions unrelated to other conditions, or, in approximately one third of the cases, in association with other abnormalities of ENS.<sup>9,13</sup> Lesions having a linear configuration and midline location, like those seen in our patient, are characteristic of ENS.<sup>2,5,14</sup> Although involvement of other organ systems was not evident, this is not unusual because the proportion of cases showing the fully developed syndrome is small.<sup>5</sup>

Oral involvement in ENS may often be overlooked.<sup>15</sup> The most common manifestations are localized or diffuse verrucous growths on the lips, palate, gingiva, buccal mucosa, and tongue.<sup>1,2,5,11,15-17</sup> Other findings include hypertrophy of the tongue, cleft palate, high arched palate, and various dental anomalies, such as hypodontia, unerupted teeth, malformed teeth, and odontodysplasia.<sup>1,2,11,15-17</sup> Oral lesions are usually located on the left side of the oral cavity and in the midline,<sup>15,16</sup> as in the case presented.

The palatal lesion in our patient is identical to previously described verrucous palatal nevi in association



Fig 6. Panoramic radiograph shows large and irregular radiolucent lesion from right canine to left second premolar.

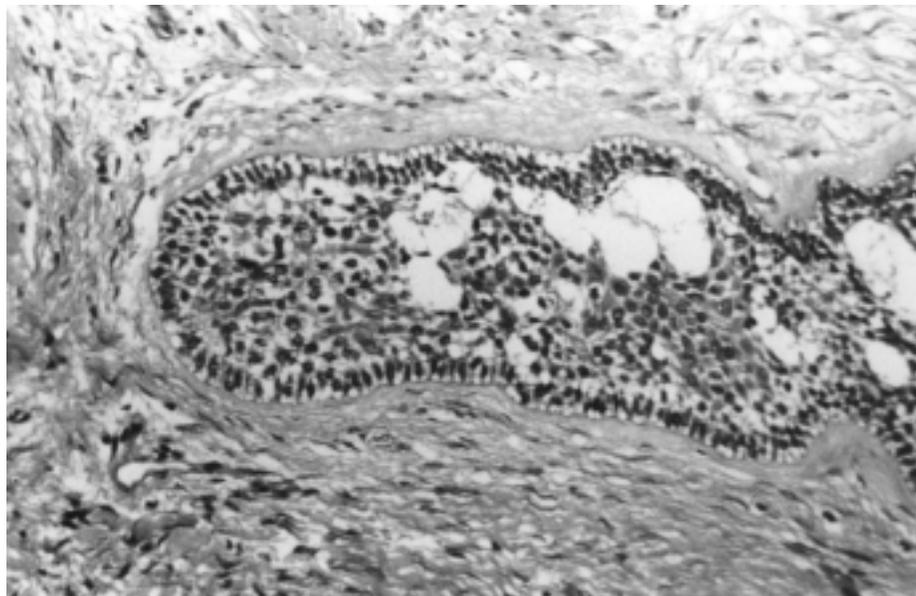


Fig 7. Epithelial island consisting of reticulum-like and acanthomatous cells. Peripheral cells show palisading, reverse nuclear polarity and cytoplasmic vacuolization (hematoxylin-eosin, original magnification  $\times 130$ ).

with facial epidermal nevi in patients with ENS.<sup>16,17</sup> Similar lesions confined to the oral cavity have been termed *papillary intraoral epithelial nevi*.<sup>16</sup> The patient's gingival lesions show strong similarity to the clinical and histologic features of the recurrent gingival nevus reported by Reichart et al.<sup>11</sup> The early age of onset, the resistance to surgical excision, and the histo-

logic characteristics of these lesions are consistent with the inflammatory type of linear epidermal nevus, a clinical and histopathologic variety of epidermal nevus<sup>18-20</sup> that may be a component of ENS.<sup>21</sup> The alterations in the keratinization pattern, considered diagnostic of this type of nevus, were not identified, but such alterations are not found in each biopsy spec-

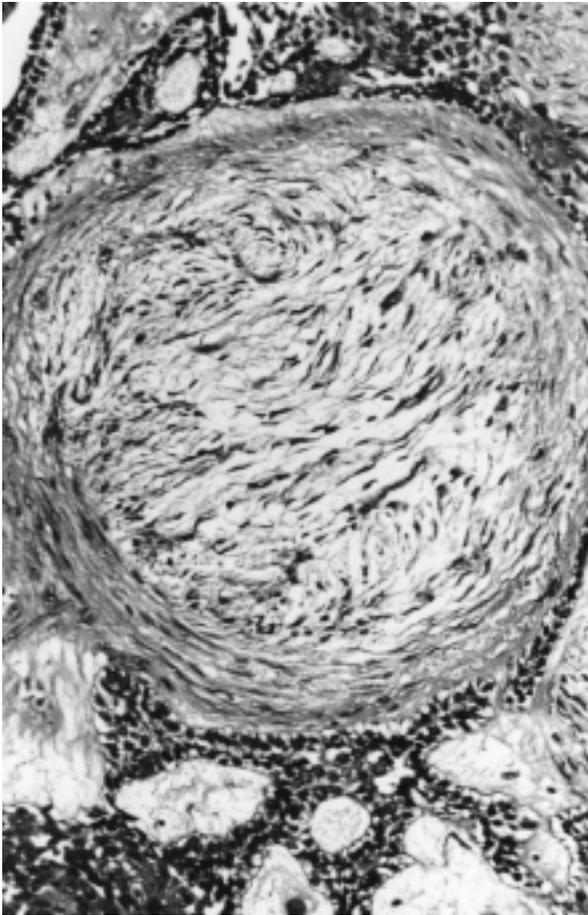


Fig 8. Globular myxomatous connective tissue areas in proximity to neoplastic epithelium (hematoxylin-eosin, original magnification  $\times 63$ ).

imen.<sup>20</sup> Furthermore, the keratinization pattern of the oral epithelium is different from that of the skin.

The proximity of the gingival lesions to fixed prosthetic restorations in this case, as well as the presence of heavy dental plaque and calculus on the teeth adjacent to the lesion reported by Reichart et al,<sup>11</sup> may not be coincidental. Local inflammatory factors are usually abundant in both situations and, as Morioka<sup>22</sup> suggested, repeated traumatic and inflammatory factors may stimulate the proliferation of the germ cells both inside and outside a nevus.

Neoplasms associated with ENS include tumors of the epidermal appendages, the genitourinary system, the central nervous system, and the gastrointestinal system, as well as lipoma, mammary adenocarcinoma, endometrioma, chondroma, and salivary gland adenocarcinoma.<sup>3,5</sup> Jaw tumors reported in patients with ENS include ameloblastoma,<sup>14,23</sup> odontoma, and giant cell granuloma.<sup>3,24</sup>

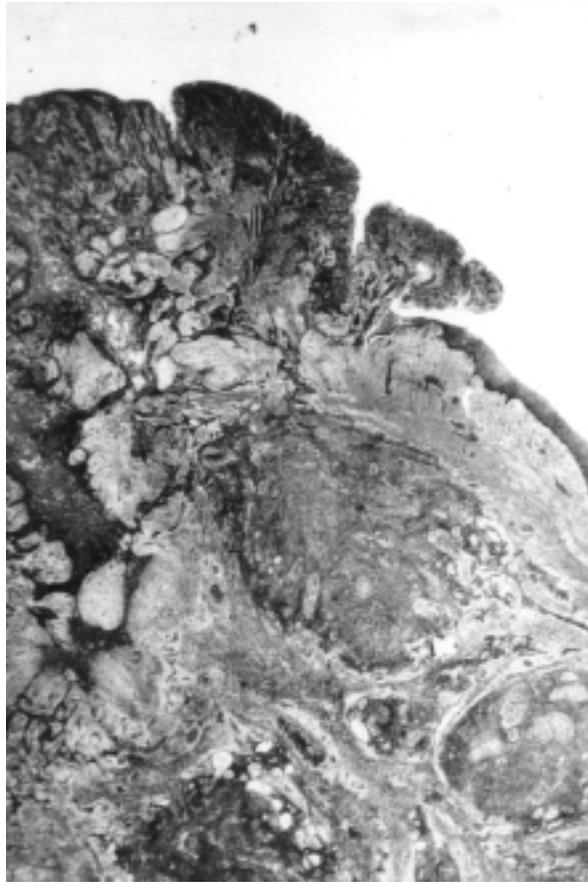


Fig 9. Papillary projections of covering epithelium are in direct continuity with tumor islands in many areas (hematoxylin-eosin, original magnification  $\times 10$ ).

A mandibular ameloblastoma was described by Lovejoy and Boyle<sup>14</sup> in a 5½-year-old boy who had linear midline sebaceous nevi (including the upper and lower lips), no neurologic abnormalities (except for an elevated unidentified cerebrospinal fluid protein), and normal cognitive development. Burck et al<sup>23</sup> reported the occurrence of ameloblastoma in a 14½-year-old girl with unilateral, partly depigmented, partly hyperpigmented atrophic skin lesions, hypertrichosis, postauricular nodules, cataracts, mild mental retardation, optic glaucoma, psammomatous meningioma, and nodules in the midline in the hard palate. The latter case was accepted as ENS by Hodge et al,<sup>3</sup> but not by Grebe et al.<sup>4</sup> The clinical and pathologic descriptions of the tumors in both cases were not provided. It seems that our case is the second report of ENS associated with ameloblastoma in the literature so far.

Ameloblastoma can conceptually arise from the ectodermally derived odontogenic epithelium or pluripotential germ cells of the basal layer of the oral epithelium.<sup>25</sup>



Fig 10. Gingival mucosa, showing areas of acanthosis and spongiosis with microabscesses formation. Connective tissue is densely infiltrated by inflammatory cells (hematoxylin-eosin, original magnification  $\times 63$ ).

Thus, it may be histogenetically related to epidermal nevi and the associated secondary tumors.<sup>26,27</sup> Whether ameloblastoma represents a low-frequency manifestation of the neoplastic potential of the syndrome or simply an incidental finding in ENS<sup>11</sup> remains to be elucidated.

Microscopic changes resembling adenomatoid odontogenic tumor, that is, duct-like cystic spaces, were evident in our tumor. Similar findings within the wall of unicystic ameloblastomas of the anterior mandible have been considered to be representative of the differentiation potential of ameloblastic epithelium.<sup>28</sup> In addition, this tumor showed multifocal continuity with the surface epithelium, which in transitional areas displayed signs of activation, that is, elongated rete ridges and hyperchromatic basal cells. This association is reminiscent of the basaloid proliferation in other forms of epidermal nevi.<sup>29</sup> Thus, a histogenetic relationship of ameloblastoma with the overlying epithelial lesion cannot be excluded.

Distinguishing the presentation of our case from benign acanthosis nigricans was based on the appearance of the oral and skin lesions and the lack of involvement of the intertriginous areas. Diffuse papillomatosis of the skin and oral mucosa may also be seen in Darier's disease, but the histologic features are diagnostic.<sup>25</sup> Multiple, confluent fibroepithelial hyperplasias of the oral mucosa are seen in the majority of patients affected with the multiple hamartoma syndrome (Cowden syndrome), but most patients have a positive family history and characteristic facial trichilemmomas.<sup>25</sup>

Our patient did not have the diagnostic features of Schimmelpenning syndrome, nevus comedonicus syndrome, pigmented hairy epidermal nevus syndrome, CHILD syndrome, or Proteus syndrome, all conditions that have been distinguished from the generic ENS by Happle.<sup>10</sup> The location of the nevi in the head and neck of our patient is suggestive of sebaceous nevus syndrome, but brain and eye involvement were lacking.<sup>13</sup> Separation of sebaceous nevus syndrome from ENS remains controversial.<sup>13</sup>

Epidermal nevi are also seen in encephalocraniocutaneous lipomatosis, characterized by unilateral cutaneous and ophthalmologic lesions and severe neurologic involvement.<sup>1</sup> The cutaneous lesions of neurofibromatosis, McCune-Albright syndrome, and Jaffe-Campanacci syndrome are café-au-lait spots without epithelial hyperplasia, whereas with focal dermal hypoplasia (Goltz syndrome) there is thinning or absence of dermal connective tissue.<sup>1,3</sup> Finally, chondrodysplasia congenita punctata (Conradi's syndrome) is usually lethal before the first year of life and is distinguished by the widespread ichthyosiform skin involvement and stippled epiphyses.<sup>3</sup>

Patients with ENS must be evaluated periodically as they show a persistent predisposition for the development of tumors,<sup>3,5</sup> both inside and outside the nevi, throughout their lives.<sup>6</sup>

#### REFERENCES

1. Gorlin RJ, Cohen MM, Levin LS. Syndromes of the head and

- neck. 3rd edition. Oxford monographs on medical genetics No. 19. Oxford: Oxford University Press; 1990. p. 362-6.
2. Solomon LM, Fretzin DF. The epidermal nevus syndrome. *Arch Dermatol* 1968;97:273-85.
  3. Hodge JA, Ray MC, Flynn KJ. The epidermal nevus syndrome. *Int J Dermatol* 1991;30:91-8.
  4. Grebe TA, Rimsza ME, Richter SF, Hansen RC, Hoyme HE. Further delineation of the epidermal nevus syndrome: two cases with new findings and literature review. *Am J Med Genet* 1993;47:24-30.
  5. Zaremba J. Jadassohn's nevus phakomatosis: 2. A study based on a review of thirty-seven cases. *J Ment Defic Res* 1978;22:103-23.
  6. Kousseff BG. Hypothesis: Jadassohn nevus phakomatosis: A paracrinopathy with variable phenotype. *Am J Med Genet* 1992;43:651-61.
  7. El-Shanti H, William EB, Waziri MH. Epidermal nevus syndrome: Subgroup with neuronal migration defects. *J Child Neurol* 1992;7:29-34.
  8. Happle R. How many epidermal nevus syndromes exist? A clinicogenetic classification. *J Am Acad Dermatol* 1991;25:550-6.
  9. Rogers M. Epidermal nevi and the epidermal nevus syndromes: a review of 233 cases. *Pediatr Dermatol* 1992;9:342-4.
  10. Happle R. Epidermal nevus syndromes. *Semin Dermatol* 1995;14:111-21.
  11. Reichart PA, Lubach D, Becker J. Gingival manifestation in linear nevus sebaceous syndrome. *Int J Oral Surg* 1983;12:437-43.
  12. Happle R. Cutaneous manifestation of lethal genes. *Hum Genet* 1986;72:280.
  13. Dodge NN, Dobyns WB. Agenesis of the corpus callosum and Dandy-Walker malformation associated with hemimegalencephaly in the sebaceous nevus syndrome. *Am J Med Genet* 1995;56:147-50.
  14. Lovejoy FH, Boyle WE. Linear nevus sebaceous syndrome: report of two cases and a review of the literature. *Pediatrics* 1973;52:382-7.
  15. Brown HM, Gorlin RJ. Oral mucosal involvement in nevus unius lateris (Ichthyosis Hystrix). A review of the literature and report of a case. *Arch Dermatol* 1960;81:509-15.
  16. Hickman RE, Eveson JW, Cawson RA. Nevus unius lateralis and intraoral verrucous nevi. *Oral Surg Oral Med Oral Pathol* 1988;66:226-9.
  17. Kelley JE, Hibbard ED, Giansanti JS. Epidermal nevus syndrome. Report of a case with unusual oral manifestations. *Oral Surg Oral Med Oral Pathol* 1972;34:774-80.
  18. Kaidbey KH, Kurban AK. Dermatitic epidermal nevus. *Arch Dermatol* 1971;104:166-71.
  19. Altman J, Mehregan AH. Inflammatory linear verrucous epidermal nevus. *Arch Dermatol* 1971;104:385-9.
  20. Dupre A, Christol B. Inflammatory linear varicose epidermal nevus. A pathologic study. *Arch Dermatol* 1977;113:767-9.
  21. Golitz LE, Weston WL. Inflammatory linear verrucous epidermal nevus. Association with epidermal nevus syndrome. *Arch Dermatol* 1979;115:1208-9.
  22. Morioka S. The natural history of nevus sebaceous. *J Cutan Path* 1985;12:200-13.
  23. Burck U, Arnold H, Siebert J. Unilateral skin lesions associated with multiple neoplasms. *Dermatologica* 1984;168:78-81.
  24. Kaplan I, Metzker A, Calderon S. Epidermal nevus syndrome with maxillary involvement. *Int J Oral Maxillofac Surg* 1993;22:298-300.
  25. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and maxillofacial pathology. Philadelphia: WB Saunders Company; 1995. p. 512-20, 541-93.
  26. Lever WF, Schaumburg-Lever G. Histopathology of the skin. 7th ed. Philadelphia: JB Lippincott Company; 1990. p. 524-5.
  27. Iglesias Zamora ME, Vazquez-Doval FJ. Epidermal nevi associated with trichilemmal cysts and chromosomal mosaicism. *Br J Dermatol* 1997;137:821-4.
  28. Raubenheimer EJ, van Heerden WFP, Noffke CEE. Infrequent clinicopathological findings in 108 ameloblastomas. *J Oral Pathol Med* 1995;24:227-32.
  29. Wilson Jones E, Heyl T. Nevus sebaceous. A report of 140 cases with special regard to the development of secondary malignant tumors. *Br J Dermatol* 1970;82:99-117.

*Reprint requests:*

Euterpe Bazopoulou-Kyrkanidou  
Department of Oral Pathology & Surgery  
Faculty of Dentistry, University of Athens  
2, Thivon St, 115 27 Athens, Greece