Vol. ■ No. ■ Month 2016

Idiopathic gingival papillokeratosis with crypt formation, a report of 7 cases of a previously undescribed entity: possible unusual oral epithelial nevus?

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We report 7 cases of hitherto undescribed keratotic papillary plaques of uncertain etiology involving the gingiva. All 7 cases presented on the anterior maxillary attached gingiva of patients in the second decade. The lesions were asymptomatic and 86% (6 of 7 cases) presented in a bilateral symmetric distribution. Microscopically, the lesions exhibited parakeratosis and papillary acanthosis with parakeratin-filled crypts. No specific etiology such as a factitial habit or a common exogenous agent has been identified. The possibility of a developmental etiology such as an oral epithelial nevus cannot be entirely excluded. We propose the descriptive term idiopathic gingival papillokeratosis with crypt formation (IGPC) for this condition. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;■:1-7)

Many oral epithelial lesions are keratotic and exhibit a papillary configuration; these include squamous papilloma, verruca vulgaris, localized juvenile spongiotic gingival hyperplasia, verruciform xanthoma, and warty dyskeratoma.[1-5] All of these occur as discrete unilateral lesions. Those that form crypts are less common and include seborrheic keratoses of the perioral skin and acanthosis nigricans.[6,7]

Much less common are oral epithelial nevi that are associated with overlying epidermal nevi.[8-11]

The objective of this study is to describe the clinical and histopathologic features of an unusual mucosal lesion that occurred on the attached gingiva of 7 young patients, and to postulate on its etiopathogenesis.

CASE REPORTS

Seven patients have been identified exhibiting an as-yet unreported finding of gingival papillary keratosis with crypt formation of unknown etiology. The clinical findings not outlined below are presented in Table I.

Case 1

A 17-year-old male presented with an asymptomatic yellowish-white, fairly well-demarcated plaque with a rough surface measuring 1.4 × 0.3 cm, involving the labial maxillary attached gingiva in the region of teeth #6-7 and terminating at the mucogingival junction. A similar lesion on the contralateral side in the region of teeth #10-11 measuring 0.8 × 0.6 cm was present, and these had been noticed for 2 years (Figure 1). Gentle wiping with gauze readily liberated superficial keratinaceous debris, leaving irregular pink papillary plaques. An incisional biopsy of the right plaque was performed.

Case 2

A 16-year-old female presented with an asymptomatic, well-demarcated white plaque of unknown duration, measuring 1.4 × 0.5 cm, with a rough surface contour, involving the labial maxillary attached gingiva extending from the midfacial aspect of tooth #6 to the mesial aspect of tooth #8. A similar lesion was noted extending from the midfacial aspect of tooth #10 to the mesial aspect of tooth #11. (Figure 1). A biopsy was obtained from the lesion on the right side.

Case 3

A 13-year-old female presented with multiple asymptomatic white demarcated plaques, measuring 0.3 cm × 0.3 cm, on the labial maxillary attached gingiva along the mucogingival junction in the region of tooth #7 (Figure 1). Similar faint white plaques were present on the opposite side symmetrically, involving the attached gingiva of teeth #10-11. The lesions were mildly sensitive, particularly when consuming hot or spicy foods, and had been present for at least 1 year. Rubbing the lesion with a cotton swab or gauze diminished the white coloration (Figure 2); however, a "velvety" irregular plaque persisted, which reestablished a white coloration over the course of a day or two. A biopsy was obtained from the plaque on the right side.

Statement of Clinical Relevance

We have identified an as-yet unreported finding of gingival papillary keratosis with crypt formation of unknown etiology. Knowledge of this previously unrecognized entity will facilitate identification of additional patients with such lesions and may help to establish whether these lesions are oral epithelial nevi or represent an acquired condition caused by local factors.

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Received for publication Jun 20, 2016; returned for revision Sep 7, 2016; accepted for publication Oct 21, 2016.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2016.10.018

Table I. Characteristics of patients presenting with IGPC

Patient	*Age/gender/race*	*Uni-/bilateral*	*Skin findings*	*Medical history/meds*	*Allergies*	*Dentifrices/habits/ appliances*	*Follow-up*
Case 1	17/M/Caucasian	Bilateral	No	Asthma/corticosteroid inhaler/acne treated with topical clindamycin	No known allergies	Crest ProHealth, Arm and Hammer toothpaste/ orthodontic retainer nightly/denies mouth breathing	Present unchanged at 3-y follow-up
Case 2	16/F/Hispanic	Bilateral	No	No systemic medications/ incidental finding of geographic tongue	Peanut allergy	No habits/no appliances	No follow-up available
Case 3	13/F/Caucasian	Bilateral	No	No systemic medications; topical dexamethasone solution 0.5 mg/ 5 mL used to treat lesions without success	Benzocaine	Colgate regular formulation/ regularly chews various brands of gum, including Extra and Trident (various flavors), and occasionally rubs the lesions with a cotton swab/ no appliances/ denies mouth breathing	Present unchanged at 1-y follow-up
Case 4	13/F/Caucasian	Unilateral	No	Intellectual disability/ no systemic medications/subtle gingival fibrous hyperplasia in the regions of teeth #7 and #10	No known allergies	Uses a variety of toothpastes/no habits/no appliances	Excised without recurrence even though lesional tissue was present at margins
Case 5	20/M/Caucasian	Bilateral	No	No systemic medications	No known allergies	Crest 3-D white/ historically placed smokeless tobacco (Copenhagen Straight) in maxillary vestibule/ wears Shock Doctor brand mouth guard for sports	Present unchanged at 3-y follow-up
Case 6	20/M/Caucasian	Bilateral	No	No systemic medications	No known allergies	Occasionally brushes the lesions with his toothbrush/no appliances	No follow-up available
Case 7	13/F/Caucasian	Bilateral	No	No systemic medications	No known allergies	No habits/no appliances	Present unchanged at 1-y follow-up

Case 4

A 13-year-old female presented with an asymptomatic rough white plaque measuring 0.6 × 0.2 cm involving the labial attached gingiva near the apical aspect of tooth #10. An excision was performed.

Case 5

A 20-year-old male presented with asymptomatic rough white plaques measuring 0.3 × 0.1 cm involving the bilateral maxillary labial attached gingiva. The patient's history was significant for placement of smokeless tobacco in the maxillary vestibule for approximately 1 year. The patient also routinely used a maxillary mouth guard when playing sports. A biopsy was obtained from the lesion on the right side.

Case 6

A 20-year-old male presented with an asymptomatic pebbly white plaque measuring 0.5 × 0.2 cm involving the maxillary labial attached gingiva in the region of teeth #7-10. The patient admitted to intermittently brushing the area with his toothbrush, as this activity helped to temporarily remove the whiteness and restore the pink coloration of the tissue. A biopsy was obtained from the right plaque.

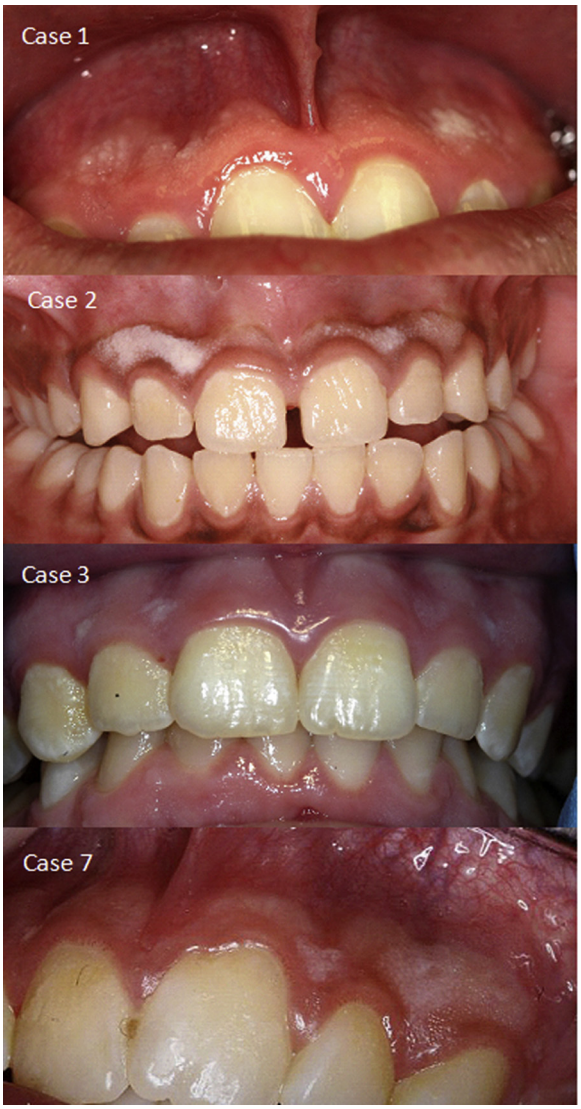

Fig. 1. Asymptomatic yellowish-white, relatively well-demarcated plaques with irregular surface contour involving the labial anterior maxillary attached gingiva.

Case 7

A 13-year-old female presented for evaluation of an asymptomatic white plaque with irregular surface contour measuring approximately 0.3 × 0.4 cm on the maxillary labial gingiva in the region of tooth #7. A similar lesion was present on the contralateral side (Figure 1). A biopsy was obtained from the lesion on the right side.

Histopathologic findings

The histopathologic features showed gingival mucosa exhibiting a thin layer of parakeratin with papillary acanthosis and multifocal epithelial crypt-like invaginations with parakeratin plugging (Figure 3). Rete ridges were long and tapered, and there were rare mitotic figures and no epithelial atypia. There were no koilocytes or other human papillomavirus (HPV)-associated cytopathic effects or dyskeratosis. The lamina propria did not exhibit significant inflammation. In situ hybridization studies for high- and low-risk human papillomavirus performed on case 2 were negative. Immunohistochemical studies for Ki-67 showed positivity in approximately 40% of basal and parabasal epithelial cell nuclei, with lower labeling seen in the basal layer and higher labeling seen in the parabasal epithelial cell nuclei, in keeping with previous findings of otherwise unremarkable oral mucosa (Figure 4).[12,13]

Follow-up

Five of the 7 cases had follow-up, and of these, 4 had persistent lesions at 1- to 3-year follow-up periods (Table I). Case 4 showed no recurrence or residual lesion 4 years after the biopsy when she returned for extractions, despite the margins of the excision being involved by lesional tissue.

DISCUSSION

We report a hitherto undescribed entity characterized by rough yellow-white plaques exhibiting a bluntly papillary architecture localized to the labial attached gingiva along the mucogingival junction. The lesions appear to exclusively affect the maxillary attached gingiva of both male (3) and female (4) patients in the second decade, with 6 of 7 cases (86 %) presenting bilaterally. The plaques spared the marginal gingiva, and all were present at the mucogingival junction. Gentle wiping of the lesion with a cotton swab or gauze (cases 1 and 3) or brushing the area (case 6) sometimes liberated accumulated parakeratinaceous debris collected within the epithelial crypts, causing the lesion to temporarily lose its white coloration. Over a short period of time, the yellow-white coloration was restored, with accumulation of parakeratinaceous debris within the crypts.

Histopathologic examination revealed parakeratotic stratified squamous epithelium exhibiting a distinctive undulating papillary architecture with crypt formation and elongated, tapered rete ridges. The epithelial invaginations contained parakeratinaceous debris. The underlying connective tissue was densely collagenous without inflammation. None of the cases exhibited koilocytes or HPV cytopathic effects, but because of the papillary nature of the lesion, in situ hybridization studies for common low-risk and high-risk HPV were performed on 1 case (case 2) and these were negative; however, as these studies are not 100% specific, the possibility of an HPV-associated etiology cannot be entirely excluded.

No specific etiology could be identified. All patients denied routine consumption of candies or specific foods and beverages, and only 1 patient (case 3) routinely chewed gum. No common oral hygiene products, including mouth rinse, could be identified,

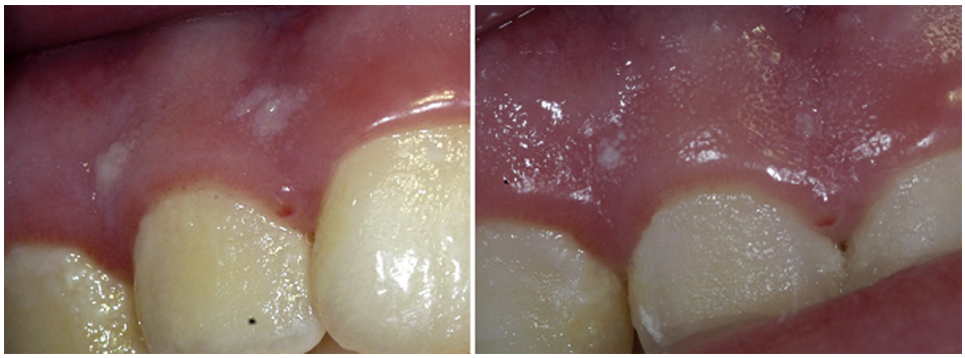

Fig. 2. Case 3 original presentation (left); wiping the lesions with gauze (right) temporarily liberates keratin plugs within the epithelial invaginations.

and at least 1 patient switched toothpaste, without improvement in the gingival condition. One patient reported use of an orthodontic appliance and another use of a sports mouth guard. One patient had placed smokeless tobacco in the maxillary vestibule, and discontinuing the habit for over 1 year did not lead to resolution, as would be expected. Furthermore, the histopathologic features were not compatible with those seen in smokeless tobacco keratosis. Although all denied a factitial habit, at least 2 admitted to brushing or wiping the area at frequent intervals in an effort to restore the pink coloration of the affected tissue. One patient reported sensitivity of the affected area, particularly when consuming spicy foods, and treatment with topical corticosteroid failed to provide symptomatic relief. One patient was reported to show complete lesional resolution at a follow-up visit approximately 4 years after excisional biopsy when she returned for extraction of her impacted third molars.

The differential diagnosis of a papillary lesion of the oral mucosa is fairly limited and includes squamous papilloma, verruca vulgaris, localized juvenile spongiotic gingival hyperplasia (LJSGH), verruciform xanthoma, warty dyskeratoma, and, less commonly, acanthosis nigricans and oral epithelial nevi. The clinical and histopathologic features of each lesion from the differential diagnosis were considered in the context of the present cases.

Squamous papilloma and *verruca vulgaris* both present usually as solitary pink-to-white and often pedunculated exophytic lesions with characteristic surface projections that impart a warty appearance.[2,4] Squamous papilloma shows a benign papillary proliferation of stratified squamous epithelium with variable keratosis overlying fibrovascular connective tissue cores, whereas verruca vulgaris exhibits prominent hyperkeratosis with hypergranulosis, koilocytosis, and a distinctive axial inclination of the epithelial rete ridges. IGPC typically presents as multifocal plaque-like lesions localized to the labial attached gingiva with diffuse papillary acanthosis and deep crypts with parakeratin plugs that impart a yellow-white color to the lesion. *LJSGH* is characterized by well-demarcated, erythematous, velvety to papillary plaques located on the facial or interproximal gingiva of patients predominantly in the second decade. Thought to represent exteriorized junctional or sulcular epithelium, LJSGH is notable for bleeding on subtle provocation and a propensity for maxillary gingival involvement.[3] Histopathologic features show nonkeratinized acanthotic stratified squamous epithelium exhibiting papillomatosis, spongiosis, and leukocyte (usually neutrophilic) exocytosis with numerous congested and dilated capillaries and an associated mixed inflammatory cell infiltrate. While both LJSGH and IGPC have a propensity for involving the maxillary gingiva of patients in the second decade, IGPC is clinically yellow-white in coloration, is not vascular, and does not exhibit spongiosis or inflammation.

Verruciform xanthoma typically presents in adults over the age of 40 years and affects the attached gingiva and palatal mucosa. It is yellow to white and usually a solitary lesion, although may be infrequently multifocal, and may be seen in the context of other epithelial disturbances such as lichen planus, pemphigus vulgaris, epithelial dysplasia, or chronic graft-versus-host disease.[5] The histopathologic features of verruciform xanthoma are characterized by papillomatosis with acanthosis and confluent rete ridges penetrating to a uniform depth. The surface is covered by a thick layer of parakeratin notable for a distinctive orange-staining tinctorial quality, with parakeratin plugging of epithelial invaginations and aggregates of foamy macrophages (xanthoma cells) within the connective tissue papillae. Although IGPC presents as a papillary yellow-white lesion, unlike verruciform xanthoma, it initially presents in young patients and appears to exclusively involve the maxillary labial gingiva.

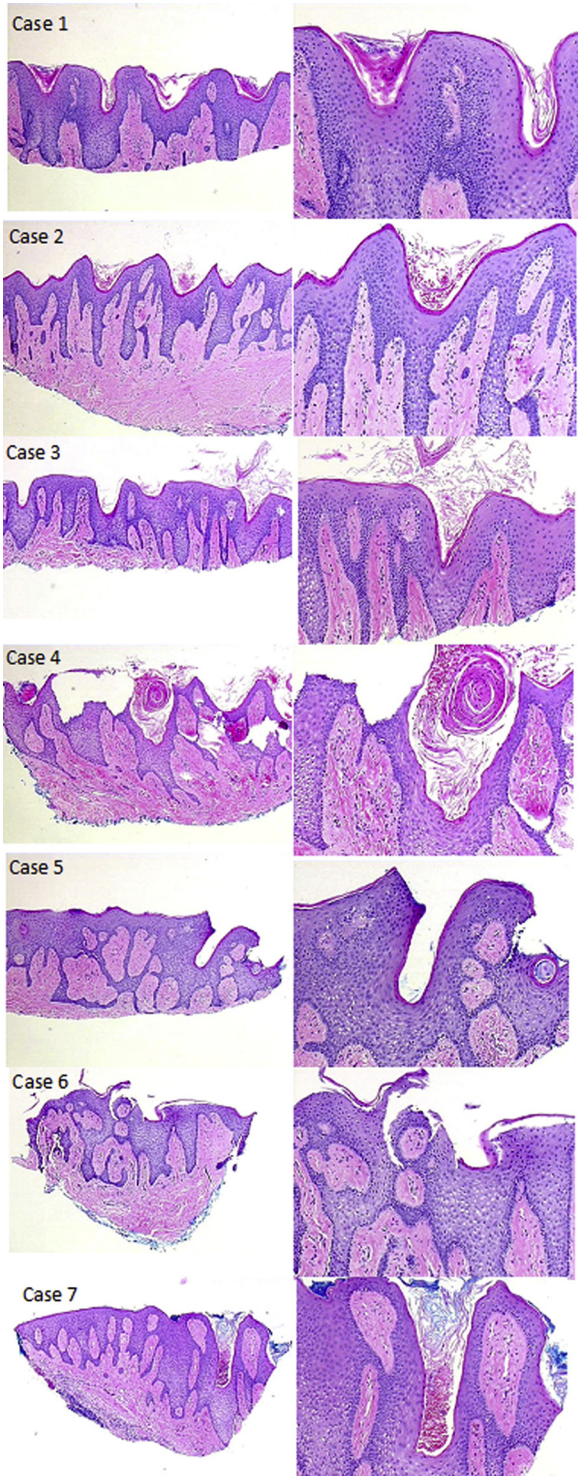

Fig. 3. Gingival mucosa exhibiting a thin layer of parakeratin with papillary acanthosis, elongated, tapered rete ridges, and multifocal epithelial crypt-like invaginations with parakeratin plugging; ×40 (left) and ×100 (right) magnification. A high-resolution version of the slide from case 3 for use with the Virtual Microscope is available as eSlide VM03106.

IGPC lacks the distinctive histopathologic findings of orange-staining parakeratin and aggregates of foamy macrophages within the connective tissue papillae that characterize verruciform xanthoma.

Acanthosis nigricans is a mucocutaneous condition characterized by velvety plaques involving the flexural aspects of the dermis and, in approximately 25-50% of patients, the oral mucosa. Acanthosis nigricans can be a herald of internal malignancy, in particular gastrointestinal cancer, although it can occur independently of systemic malignant neoplasia, such as in insulin resistance, diabetes mellitus, obesity, other endocrinopathies, or hepatitis B; it can also be medication-induced. None of these findings was noted in these patients.[6,14] Oral lesions are characterized by diffuse papillary lesions predominantly involving the tongue and lips, unlike isolated involvement of the gingiva in IGPC in young patients. The histopathologic features are characterized by hyperkeratosis, acanthosis, and papillomatosis, somewhat similar to what is seen in IGPC but without crypt formation and parakeratin plugging.

Warty dyskeratoma typically presents in the fifth to seventh decade as a white rough-surfaced papule or plaque of the keratinized mucosa, most frequently involving the hard palatal and alveolar mucosa, similar to IGPC.[1] Histopathologically, warty dyskeratoma is characterized by a crateriform proliferation of acantholytic squamous epithelium exhibiting a thick irregular parakeratin plug with associated dyskeratosis and suprabasilar clefting. The epithelial rete ridges are elongated and somewhat test-tube shaped, forming basaloid cords within the lamina propria. IGPC lacks a crateriform growth pattern, dyskeratosis, acantholysis, and proliferating cords of basaloid epithelium at the base.

Because of the young age of patients and the symmetry of lesions, the possibility of a developmental anomaly such as an unusual *oral epithelial nevus* was considered. By definition, a nevus is a hamartoma of the skin and mucosa. Epidermal nevi classically present within the first year of life; however, in some instances such lesions develop later in childhood. At pubescence, such lesions often become thickened and more verrucous.[15,16] Linear epidermal nevi have rarely been reported in the oral cavity, with 14 cases reported to date.[8-11,17,18] Epidermal nevi are characterized by hyperkeratosis, papillomatosis, acanthosis, keratin plugging of epithelial invaginations, and elongation of the rete ridges, similar to the features noted in the cases reported here. We postulate that this may represent a form of unusual oral epithelial nevus because of the

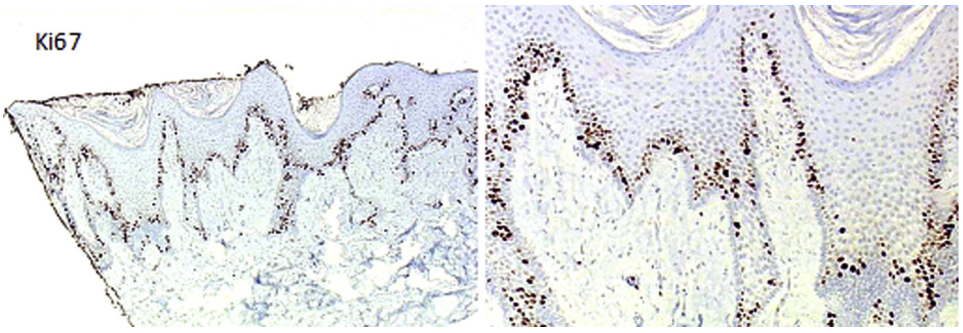

Fig. 4. Immunohistochemical studies for Ki67 showing nuclear positivity in approximately 40% of basal and parabasal epithelial cell nuclei, with lower labeling seen in the basal layer and higher labeling seen in the parabasal epithelial cell nuclei; ×40 (left) and ×100 (right) magnification.

young age at presentation, the lack of specific etiology such as a factitial habit or common exogenous agent, and the histopathologic features characterized by a benign proliferation of squamous epithelium. It is possible that these lesions were present at an earlier age but were small and not noticed until the onset of puberty led to proliferation and the lesions became more obvious. However, it is distinct from oral linear epidermal nevi as reported in the literature in its exclusive location on the maxillary gingiva, bilaterality, and lack of skin findings.[8-11] Spontaneous involution of congenital melanocytic nevi has been reported; however, such instances are typically described in the context of immune-mediated destruction of melanocytes and are often reported in the context of a halo phenomenon or vitiligo.[19] Involution of epidermal nevi, however, has not been described.

CONCLUSION

Seven patients have been identified exhibiting an as-yet unreported finding of gingival papillary keratosis with crypt formation of unknown etiology. In this series, the lesions presented exclusively in patients in the second decade, localized to the anterior maxillary attached gingiva and sparing the marginal gingiva, and stopping abruptly at the mucogingival junction. The lesions were typically bilateral and symmetric (in 6 out of 7 cases, 86%), and were characterized by yellow-white plaques with an irregular bluntly papillary undulating surface contour. Gentle wiping with a cotton swab or gauze liberated keratin plugs within the epithelial invaginations, which left a residual velvety pink plaque with persistent surface irregularity, although this was only temporary. Only 1 patient noted a mild degree of associated sensitivity. Microscopically, these benign lesions exhibited papillomatosis and acanthosis, with epithelial crypts filled with parakeratin. Identification of additional patients with such lesions may help us understand whether these represent nevi or are an acquired condition caused by local factors.

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