Solitary oral epidermolytic acanthoma: Case report of a rarely diagnosed entity

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Epidermolytic acanthoma represents a rare localized form of epidermolytic hyperkeratosis, which resembles warty lesions and shows a strong predilection for the genital skin of males. Here, we present an oral solitary epidermolytic acanthoma affecting a 71-year-old Caucasian man. Clinically, the lesion was white, well-circumscribed, and sessile, measuring 2 mm in diameter and located on the posterior mandibular buccal gingiva. Microscopically, pronounced hyperkeratosis and acanthosis, with formation of keratin crypts was observed. Lesional cells of the spinous and granular epithelial layers exhibited prominent intracellular vacuolar degeneration, as well as eosinophilic paranuclear and perinuclear condensations. Intracytoplasmic eosinophilic globules were also seen. No recurrences have been reported. Investigation for low- and high-risk human papillomavirus (HPV) infection failed to reveal positivity for HPV subtypes 6, 11, 16, and 18. Literature review revealed scarce reports of epidermolytic hyperkeratosis–like changes of the oral mucosa associated with malignant neoplasms and inflammatory processes. Epidermolytic acanthoma should be considered in the differential diagnosis of benign epithelial papillomatous lesions of the oral cavity. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:e208–e213)

The term *epidermolytic hyperkeratosis* (EHK) refers to congenital or acquired abnormality of epidermal maturation, histologically characterized by pronounced hyperkeratosis, thickened granular cell layer with coarse basophilic cytoplasmic granules, vacuolar degeneration, and eosinophilic perinuclear bands or globular inclusions in the epithelial spinous and granular cell layers.[1-3] EHK may be seen in association with bullous ichthyosiform erythroderma, palmoplantar keratodermas, ichthyosis hystrix, epidermal nevus, acrosyringial epidermolytic papulosis neviformis, and epidermolytic acanthoma (EA).[1-7] EA represents a rare localized form of EHK resembling, clinically, papillomatous epithelial proliferations.[8]

EA is uncommon and manifests usually in adults as asymptomatic, solitary (isolated) or multiple (disseminated), warty, keratotic papules.[9,10] The isolated solitary variant of EA, originally described by Shapiro and Baraf in 1970,[8] can occur anywhere on the skin, whereas the disseminated subtype, first described by Hirone and Fukushiro,[11] appears to show a predilection for the back and genitoscrotal areas and exhibits strong male predilection.[12]

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The etiology of EA is currently unknown; however, mutations in the genes encoding for cytokeratin 1 and 10 have been identified in solitary EA.[13] Exogenous factors, such as viruses (e.g., human papillomavirus [HPV]),[14] ultraviolet radiation, and trauma have been also implicated in the pathogenesis of EA.[15,16] In addition, EA occurrence has been associated with immunosuppression.[2,10,17] Focal EHK rarely occurs intraorally, and the keratinized mucosa (i.e., attached gingiva and hard palate) appears more commonly affected.[18] EHK-like features, however, have also been observed as incidental findings in clinically normal oral mucosa removed during wider excision of basal cell carcinoma of the upper lip,[19] adjacent to oral squamous cell carcinoma (SCC)[19,20] and oral erosive lichen planus.[21] In our study, we investigated the clinical and histopathologic characteristics of solitary EA affecting the alveolar gingival mucosa, as well as the presence of low- and high-risk HPV types, by using molecular and immunohistochemical techniques.

CASE REPORT

A healthy 71-year-old Caucasian male presented with a white, well-circumscribed, slightly exophytic, sessile lesion, measuring approximately 2 mm in diameter and located on the alveolar buccal gingiva between the first and second right mandibular molars (Figure 1). Microscopically, the specimen featured, centrally, a well-demarcated papular epithelial proliferation (Figures 2 and 3), characterized by pronounced compact hyperkeratosis and acanthosis, with formation of keratin crypts (see Figures 3 and 4), as well as foci of spongiosis and acantholysis (Figure 5). Lesional cells of the spinous and granular epithelial layers exhibited prominent intracellular vacuolar degeneration (see Figures 4 and 5), as well as eosinophilic perinuclear and/or paranuclear condensations (Figure 6, *black arrows*). Intracytoplasmic

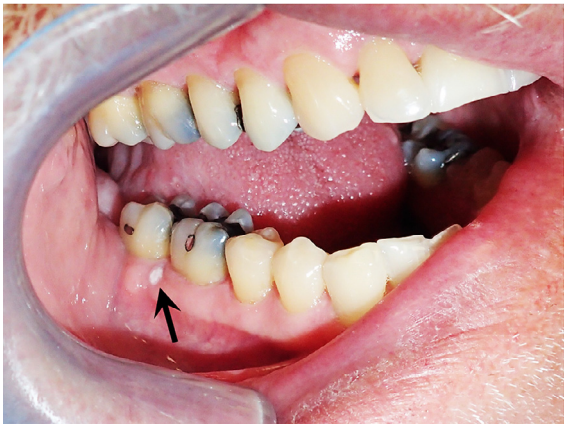

Fig. 1. Oral solitary epidermolytic acanthoma (EA) presenting as a small, white, well-circumscribed, sessile lesion of the alveolar buccal gingiva between the first and second right mandibular molars (teeth #30–#31). The black arrow indicates the exact location of the lesion.

eosinophilic globules were also observed (see Figure 6, *green arrows*). Basal cells revealed nuclear palisading and spindling, with some rare, apparently regular mitoses also present. The supporting connective tissue was characterized by fibrosis and mild to moderate and diffuse chronic inflammation. On the basis of the clinicopathologic characteristics of the lesion, a diagnosis of solitary EA of the mandibular gingiva was rendered. Postoperative recovery of the patient was uneventful, and no evidence of recurrences has been reported within a 12-month follow-up period.

Because HPV-16 has been identified in a report of multiple EAs of the scrotum,[14] we investigated for the presence of common low- and high-risk HPV types of intraoral solitary EA in the current case.

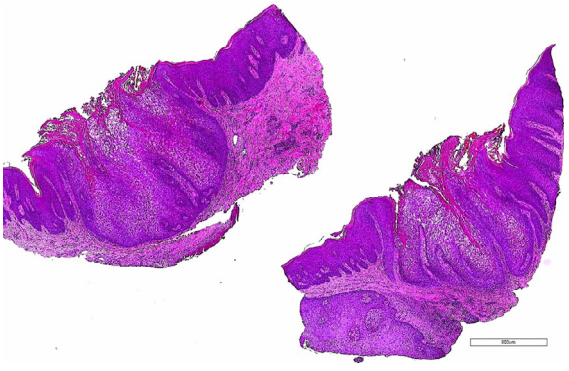

Fig. 2. Histopathologic characteristics of epidermolytic acanthoma (EA). Low-power photomicrograph of the biopsied specimen depicting oral mucosa with a centrally located, well-demarcated, endophytic epithelial proliferation (H&E; original magnification × 25). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05574.*

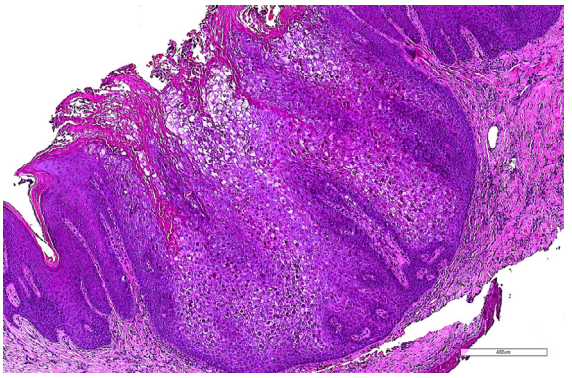

Fig. 3. Medium-power photomicrograph of the papular lesion disclosed pronounced compact hyperkeratosis and acanthosis with formation of multiple keratin crypts. The epithelial rete pegs appear elongated, thickened and interconnected (H&E; original magnification × 60). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05574.*

MATERIALS AND METHODS

HPV in situ hybridization

The presence of low-risk HPV types 6 and 11 was investigated by using in situ hybridization (ISH) with the PATHO-GENE HPV type 6/11 probe (Enzo Life Sciences, Inc., Farmingdale, NY), and for high-risk HPV, the HPV16/18 probe cocktail (Ventana Medical Systems, Inc., Tucson, AZ) was utilized. Appropriate positive and negative controls were included.

p16 immunohistochemistry

Immunohistochemical staining against p16 was performed by using a specific mouse monoclonal antibody (clone E6 H4, MTM Laboratories AG, Heidelberg, Germany) on the Ventana Nexes Automated Immunostaining Platform (Ventana Medical Systems, Inc.,

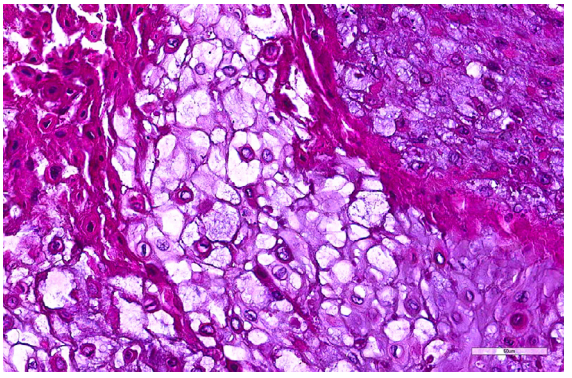

Fig. 4. High-power photomicrograph of epidermolytic acanthoma (EA) showing epithelial cells of the spinous cell layer with prominent intracellular vacuolar degeneration (H&E; original magnification × 350). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05574.*

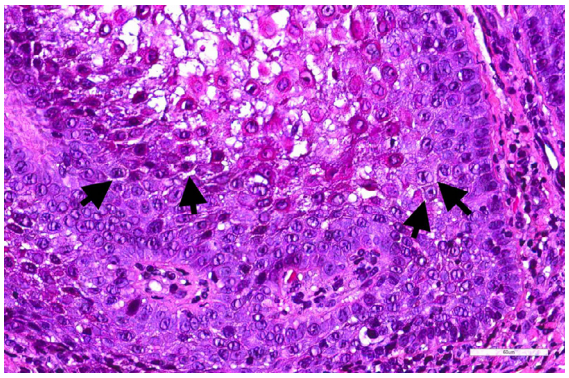

Fig. 5. High-power photomicrograph highlighting the spongiotic changes of the desmosomes (as indicated by the black arrows) in the lower third of the spinous cell layer (H&E; original magnification × 350). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05574.*

Tucson, AZ), according to the manufacturers' instructions, as reported.[22-24] An appropriate positive control was also included. Continuous and diffuse nuclear and cytoplasmic immunoreactivity in greater than 75% of lesional cells was considered positive.

HPV DNA polymerase chain reaction

Polymerase chain reaction (PCR) detection of HPV DNA was performed in a CLIA (Clinical Laboratory Improvement Amendments)−certified molecular diagnostics laboratory (University of Minnesota, Minneapolis, MN). Routine sensitivity testing, which is performed on a quarterly basis, consistently demonstrated a limit of detection of 250 copies of the HPV viral genome. DNA was extracted from the formalin-fixed, paraffin-embedded tissue block by using the DNeasy tissue kit (Qiagen, Valencia, CA, USA), according to manufacturer's protocols. Amplification of HPV DNA was performed by using the MY09/11 primers for the L1 conserved region (MY11: 5′GCM CAG GGW CAT AAY AAT GG-3′; MY09: 5′ CGT CCM ARR GGA WAC TGA TC-3′; where Y = C,T; R = A,G; M = A,C; W = A,T at the degenerate nucleotide sites) in a duplexed PCR reaction, with primers for human beta-globin as an internal control (Fwd: 5′ GAA GAG CCA AGG ACA GGT AC-3′; Rev: 5′ CAA CTT CAT CCA CGT TCA CC-3′). PCR amplification was carried out for 35 cycles by using Amplitaq polymerase (Life Technologies, Grand Island, NY) under the following conditions: denaturation 94°C 30', annealing 53°C 30', and extension 72°C 30'. PCR reaction products were analyzed on a QIAxcel multicapillary gel electrophoresis system (Qiagen, Valencia, CA). Expected product sizes were HPV L1 region: 450 base pairs (approximate); and beta-globin: 268 base pairs. The positive control consisted of HPV type 16 DNA (World Health Organization International Standard) mixed with HPV-negative human DNA to a dilution representative of 2 copies of the HPV genome/diploid cell. Positive samples were then restriction digested by using PstI, RsaI, and HaeIII (New England Biolabs, Ipswich, MA) in separate reactions, and restriction fragment length polymorphism products were separated by polyacrylamide gel electrophoresis with ethidium bromide staining for genotype interpretation by a pathologist, as previously reported.[22-24]

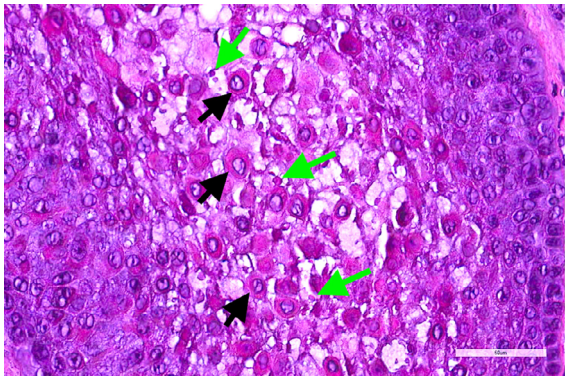

Fig. 6. High-power photomicrograph showing eosinophilic, perinuclear, band-like condensations *(black arrows)* and intracytoplasmic eosinophilic globules *(green arrows)* (H&E; original magnification × 400). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05574.*

RESULTS

The lesion was negative for low-risk HPV types 6 and 11 (Figure 7A) and showed equivocal reactivity for HPV types 16 and 18 by DNA ISH (Figure 7B), with scattered lesional (see Figure 7B, *black arrows*) and nonlesional cells exhibiting weak nuclear positivity. We further assessed high-risk HPV positivity by using p16 immunohistochemistry (Figure 8) and HPV DNA PCR (Figure 9). Both assays were negative for the presence of transcriptionally active HPV infection.

DISCUSSION

After review of the literature utilizing the PubMed portal and the keywords "oral epidermolytic acanthoma" and "oral epidermolytic hyperkeratosis," we did not find any well-documented case of oral solitary EA. The reasons for the apparent lack of reported cases of oral EA may be its rarity because of differences in keratinization of oral and cutaneous epithelia,[20] and overlapping clinicopathologic features with squamous papillomas or other warty proliferations, which can lead to misinterpretation.[12,20]

The clinical differential diagnosis of solitary EA includes other intraoral mucosal lesions with similar papillomatous or verrucous features, such as squamous

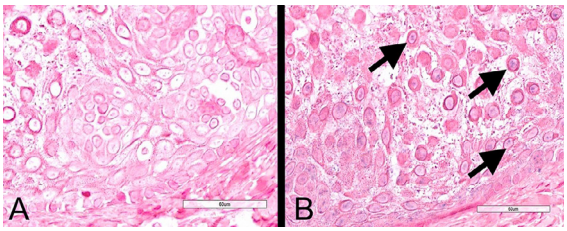

Fig. 7. **(A)** Human papillomavirus (HPV) in situ hybridization (ISH) was negative for low-risk HPV types 6 and 11. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05575.* **(B)** HPV ISH for high-risk HPV types 16 and 18 was considered equivocal; some scattered lesional cells *(black arrows)* exhibited weak nuclear positivity. Similar reactivity was seen in nonlesional cells as well. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05576.*

papilloma and verruca vulgaris, warty dyskeratoma, and molluscum contagiosum. The microscopic features of EA distinguish it from common warts and molluscum contagiosum. However, in our opinion, warty dyskeratoma may pose some difficulty in the histopathologic differential diagnosis. In patients older than 40 years of age, intraoral warty dyskeratoma develops as a pink or white umbilicated papule that shares histopathologic features with lesions of keratosis follicularis (i.e., dyskeratosis, basilar hyperplasia, and intraepithelial clefting).[25] Notwithstanding other microscopic similarities, clefting is not typically seen in EA, and the spinous epithelial cells show vacuolar degeneration and cytoplasmic perinuclear condensations, which are not features of warty dyskeratoma.[26]

The histopathologic characteristics of solitary genital EAs, delineated in the study by Kazlouskaya et al.[2] include (1) well-circumscribed, cup-shaped lesions with a papillomatous or flat base (acanthotic and polypoid

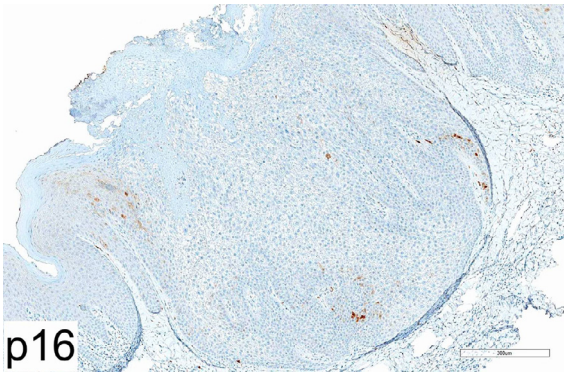

Fig. 8. Solitary epidermolytic acanthoma (EA) of the oral cavity was negative for the human papillomavirus surrogate marker p16 by immunohistochemistry (original magnification × 80). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05577.*

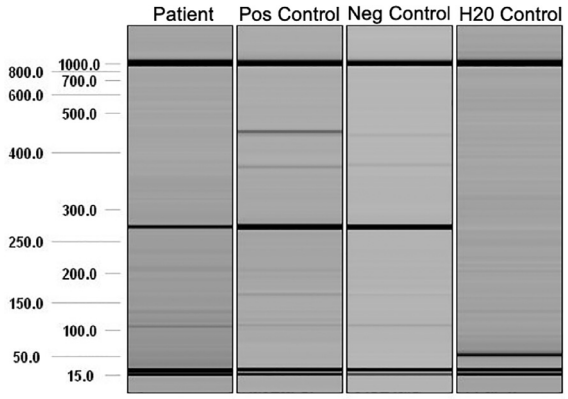

Fig. 9. Patient sample is negative for Human papillomavirus (HPV) DNA, as shown by the MY09/11 polymerase chain reaction (PCR) assay. Base-pair (bp) sizes are indicated at the left. A lower limit of detection HPV-16 positive control (Pos Control; 1000 copies of HPV DNA) shows a L1-HPV PCR product at ~450 bp. The internal control (human beta-globin) is detected in all samples except for the blank water control (~260 bp).

variants also exist); (2) perinuclear eosinophilic rim, with variably sized coarse basophilic granules, eosinophilic globules, and intercellular and intracellular edema involving all layers of the epidermis except for the basal layer; (3) frequent presence of mitotic and necrotic cells within the epidermis; (4) hyperkeratosis and, occasionally, orthokeratosis; and (5) perivascular lymphocytic inflammation at the base of the lesion. The oral solitary EA in the current case fulfilled the above criteria, with the exception of frequent mitotic activity (rare mitoses were seen at the basal cell layer) and the absence of perivascular inflammation, features that, in our opinion, are not obligatory for the diagnosis of EA.

Pertaining to the skin, it is postulated that EHK-like changes may be indications of widespread cellular damage, possibly associated with prolonged exposure to sun/ultraviolet light.[27] Specifically, in a cohort of 500 consecutive skin specimens, EHK-like changes were identified in 1.8%; all cases were diagnosed as dysplastic nevi or cutaneous malignancies.[27] Similarly, EHK-like alterations are present in the dysplastic epithelial lesions of the oral mucosa. However, cytopathologic and histopathologic variations suggestive of oral premalignant epithelial dysplasia, including enlarged nuclei and cells, increased nuclear-to-cytoplasmic ratio, nuclear pleomorphism, hyperchromasia, and abnormal mitotic figures,[28] are not present in lesions that are purely EHK or EA.

Cytologic features similar to EA can be also observed in the diffuse intraoral hyperkeratotic lesions associated with focal palmoplantar and oral mucosa hyperkeratosis syndrome,[29,30] a type of keratoderma. True focal EHK rarely involves the oral cavity. Menon and Woo[18] reported 3 cases of oral EHK affecting the

attached gingiva and hard palate of 2 females (ages 45 and 56 years) and 1 male (age 69 years). In all these cases, the lesions were not associated with other mucosal pathoses.[18] In addition, there have been scarce reports of intraoral lesions with EHK-like features in the context of neoplastic and inflammatory processes.[19-21] Four of the reported oral cases with EHK-like features were diagnosed as incidental findings in association to oral SCC,[19,20] basal cell carcinoma,[20] and erosive lichen planus.[21] Goette and Lapins[19] described 2 incidental cases of EHK in normal oral mucosa adjacent to basal cell carcinoma of the cutaneous part of the upper lip and cheek, as well as adjacent to SCC of the lip vermillion. Additionally, a case showing distinct areas of focal acantholytic dyskeratosis and EHK were reported in a 74-year old woman with SCC of the left posterior mandibular ridge.[20] The adjacent, nonneoplastic mucosa exhibited areas consistent with EHK and focal dyskeratosis. Also, EHK-like changes were reported in a 39-year old man with erosive lichen planus undergoing interferon-α-2b therapy for a chronic hepatitis C.[21] The patient developed disseminated extraoral lesions on the scalp, chest, back, buttocks, legs, and genitalia. A potential etiologic relationship, however, between EHK and interferon-α-2b therapy could not be established.[21] Finally, at this point, it is worth mentioning the article by Quinn and Young,[31] wherein 2 cases of EHK in the lower female genital tract were described. In addition to the vaginal, white, hyperkeratotic plaque consistent with EHK, one of the 2 patients also presented with white leukoplakic lesions of the oral mucosa previously diagnosed as hereditary benign intraepithelial dyskeratosis.[31] Histopathologic photomicrographs of the intraoral lesions were not provided in the report, and the hereditary trait—the father and brother of the patient also had similar plaques—and the multifocality of the lesions probably led to a diagnosis of hereditary benign intraepithelial dyskeratosis over that of EHK.

The contributory factors associated with the development of solitary EA remain unknown. Because of the wart-like appearance of EA and its strong predilection for the skin of the genitoscrotal area, HPV involvement has been hypothesized.[14] Notwithstanding the previously reported example of multiple EAs of the scrotum positive for high-risk HPV genotype 16[14] and the successful treatment of a solitary EA with imiquimod, a drug used to treat HPV-induced cutaneous lesions,[32] the etiologic role of HPV in EA has been equivocal.[2] In a study by Kazlouskaya et al.,[2] 22 anogenital EAs of the solitary type were consistently negative for low- and high-risk HPV genotypes, as shown by ISH. Furthermore, in a recent retrospective analysis[12] of 8 cases of multiple genital EAs, all of the lesions were found to be negative for the surrogate marker p16. Multiple previous attempts have failed to detect the presence of HPV in EAs of the genitalia with PCR[32] and immunohistochemistry.[31,33] The current case of solitary oral EA was also negative for low-risk HPV types 6 and 11 and high-risk types 16 and 18, as shown by ISH, HPV DNA PCR, and p16 immunohistochemistry.

Mutations in the genes encoding for cytokeratin 1 and 10 have been identified in isolated EAs.[13] Similarities at the molecular level may explain the shared clinicopathologic features between EA and inherited ichthyosis.[34] EA has occurred in immunocompromised patients as a result of kidney transplantation,[10] renal transplantation,[17] and HIV infection.[2] Furthermore, external trauma has been implicated in the etiology of solitary and disseminated EAs,[15,16] which could be the case for oral lesions as well.

CONCLUSIONS

Here, we presented the clinicopathologic characteristics and HPV status of a solitary EA affecting the oral mucosa, an apparently rare location, to raise awareness among pathologists, which would help avoid diagnostic pitfalls.

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