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ORIGINAL PAPER

Benign Alveolar Ridge Keratosis: Clinical and Histopathologic Analysis of 167 Cases

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Abstract

Benign alveolar ridge keratosis (BARK), the intraoral counterpart of cutaneous lichen simplex chronicus, is a reactive hyperkeratosis caused by trauma or friction that presents as a poorly demarcated white papule or plaque on the keratinized mucosa of the retromolar pad or alveolar ridge mucosa (often edentulous). This is a clinical and histopathologic analysis of BARK including evaluation of p53 expression in selected cases. One hundred and sixty-seven cases of BARK were identified from 2016 to 2017 and 112 (67.1%) occurred in males with a median age of 56 years (range 15–86). The retromolar pad was affected in 107 (64.1%) cases and the edentulous alveolar mucosa in 60 (35.9%) cases, with 17.4% of the cases presenting bilaterally. BARK showed hyperkeratosis often with wedge-shaped hypergranulosis and occasional focal parakeratosis. The epithelium exhibited acanthosis and surface corrugation with tapered rete ridges often interconnected at the tips. The study for p53 performed in 12 cases showed less than 25% nuclear positivity. BARK is a distinct benign clinicopathologic entity caused by friction, which should be clearly distinguished from true leukoplakia, a potentially malignant disorder.

Keywords Frictional keratosis · Leukoplakia · Oral potentially malignant disorder · Epithelial dysplasia · p53 · Cutaneous lichen simplex chronicus

Introduction

Benign alveolar ridge keratosis (BARK) is a common reactive keratotic lesion caused by chronic trauma such as from impaction of food, chronic movement of an ill-fitting denture on the gingiva or alveolar mucosa, or direct trauma from a hyper-erupted tooth [1, 2]. This distinctive clinicopathologic entity is the oral counterpart of cutaneous lichen simplex chronicus, which is a reactive keratosis resulting from chronic habitual skin scratching or picking [3]. Clinically, it presents as a poorly-demarcated white papule or plaque on the keratinized mucosa, such as the retromolar pad or edentulous alveolar ridge mucosa [1]. Histopathologically, the oral mucosa shows hyperkeratosis with wedge-shaped hypergranulosis and occasional focal parakeratosis. The epithelium exhibits mild to moderate acanthosis and surface corrugation and there is usually minimal inflammation [1].

Oral leukoplakia, on the other hand, is one of the most common oral premalignant disorders, a clinical term defined by World Health Organization in 2017 as "white plaques of questionable risk, having excluded (other) known diseases or disorders that carry no increased risk for oral cancer" [4]. Approximately 9% to 45% of leukoplakia shows dysplasia, carcinoma in situ or invasive carcinoma at the time of initial biopsy [5–7], and the malignant transformation rate of leukoplakia ranges from 1 to 18% [8–12]. This wide percentage range reported in the literature of dysplastic findings in leukoplakia may be due to the inclusion of benign or reactive keratoses such as BARK [13]. Recognizing BARK as a distinct clinical and histopathological entity is important for several reasons. Firstly, it will help to determine the true incidence of malignant transformation of leukoplakia without being diluted by reactive keratosis. Secondly, a diagnosis of BARK will spare the patient from the distress of carrying

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a diagnosis of a potentially malignant condition, and the burden of surveillance biopsies and long-term follow-up.

p53 is a well-known tumor suppressor protein that functions as the guardian of the genome. In the event of DNA damage, p53 arrests the cell cycle at G phase and blocks cell cycle progression into S phase [14]. Aberrant p53 expression has been reported in other premalignant mucosal conditions, such as cervical intra-epithelial neoplasia and vulvar dysplasia [15, 16]. In normal vulvar epithelium, expression of p53 is restricted to the basal and parabasal cell layers, while in dysplastic epithelium, p53 expression is increased and involves suprabasal layers [15]. Similarly, normal and reactive oral epithelium also exhibits p53 expression confined to the basal cell layer in less than 25% of the cells. In oral epithelial dysplasia, p53 expression increases to 60% of the basal, suprabasal and spinous layers [17–19].

The objective of this study is to further characterize the clinical and histopathologic features of a large series of BARK and analyze p53 expression pattern in the selected cases.

Materials and Methods

Cases diagnosed as BARK were identified from the archives of StrataDx, the surgical pathology laboratory affiliated with the Harvard School of Dental Medicine, between January 2016 and December 2017. The histopathological diagnostic criteria for BARK include the presence of hyperkeratosis, parakeratosis, acanthosis with or without surface corrugation and no evidence of dysplasia [1]. Demographic and clinical data were extracted from requisition forms and all slides were reviewed. Twelve cases were randomly selected for the study of p53 expression (SP5; Rabbit monoclonal antibody, Cell Marque, Rocklin, CA). Ten cases of benign reactive/frictional keratoses (morsicatio mucosae oris) served as controls.

Results

Clinical information is provided in Table 1. One hundred and sixty-seven cases of BARK were identified. There were 112 (67.1%) males and the male:female ratio was 2:1. The median age was 56 years (range 15–86 years) with the majority (85.0%) in the fifth to eighth decades (Fig. 1). Only 54 cases reported smoking status, of which 41 were current smokers, 10 were former smokers and 3 were non-smokers. The retromolar pad was the most frequently affected location in 107 patients (64.1%) and the remaining 35.9% of cases were located on the edentulous alveolar ridge mucosa, with 17.4% presenting bilaterally (Fig. 2a). Figure 2b shows a typical BARK where a tooth had been extracted. The superior aspect is the most thickly keratotic because this is the site of highest impact, with keratosis being less prominent or "fading" towards the slopes of the ridge mucosa. Fifty-five patients (32.9%) were either completely or partially edentulous and 11 cases (6.6%) occurred at the site of single tooth that had been previously extracted. Clinically, lesions were described as a white lesions, smoking-related lesions or dysplasia or carcinoma in 144 out of 154 cases (93.5%) where a clinical impression was provided, with 37 cases having a rough or papillary surface. One case showed erythematous changes, and two cases exhibited ulceration.

Table 1 Clinical features of benign alveolar ridge keratosis

Gender	
Male	112 (67.1%)
Female	55 (32.9%)
Age (years)	
Median	56
Range	15–86
Site	
Retromolar pad	107 (64.1%)
Edentulous alveolar ridge	60 (35.9%)
Bilateral	29 (17.4%)
Common clinical diagnosis[a]	
Keratosis/Leukoplakia	113 (67.7%)
Keratosis (97)	
Leukoplakia (13)	
Smoking related lesions (3)	
Dysplasia/carcinoma	31 (20.1%)
Lichen planus	3 (2.0%)
Papilloma	2 (1.3%)
Others[b]	5 (3.2%)

[a]154 out of 167 cases provided the clinical impression

[b]Other clinical diagnosis includes psoriasis and aphthous ulcer

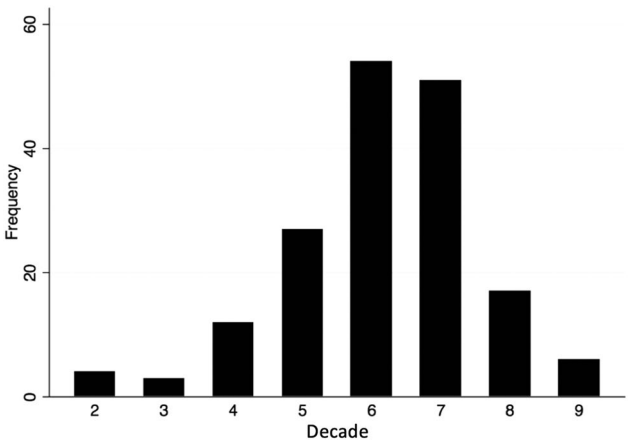

Fig. 1 Age distribution for BARK

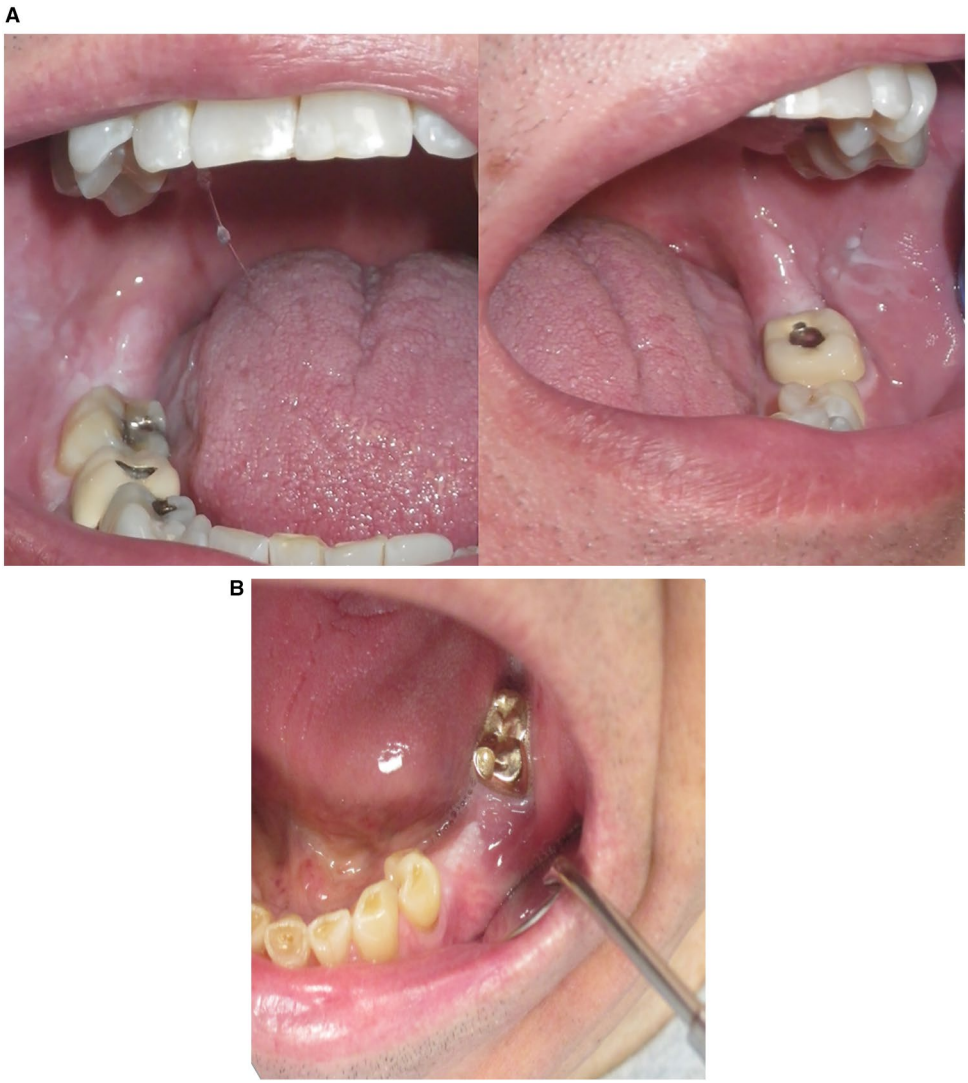

Fig. 2 **a** BARK on the retromolar pad, present bilaterally. Note the bite keratosis on bilateral buccal mucosa as well. **b** BARK at the site of previously extracted teeth; note the thick, rough keratosis on the ridge crest with tapering keratosis on the slope of the ridge

Histological features are summarized in Table 2. Hyperkeratosis with hypergranulosis was present in 161 cases (96.4%), of which 111 (69.4%) showed a wedge-shaped pattern of hypergranulosis (Fig. 3a). Focal parakeratosis was present in 39 cases (23.4%) and merely six cases (3.6%) exhibited only parakeratosis; the keratin usually had a tapering edge consistent with its clinical appearance of a "fading" margin, noted in 85 cases where the edge was included in the specimen (Fig. 3b, c). Surface corrugation was noted in 118 cases (70.6%) (Fig. 3a, d). Rete ridges in almost all cases were tapered (165 cases, 98.8%) and interconnected at the tips (163 cases, 97.6%). *No cases showed epithelial atrophy*. The evidence of adjacent or healing ulcer, i.e., intraepithelial hemorrhage with subepithelial fibrin deposition, was noted in 7 cases, which was always associated with parakeratosis (Fig. 3d). Fifteen cases exhibited bacterial colonization on the epithelial surface and it was almost always associated with focal parakeratosis (Fig. 3b). Fifty-three of the cases (31.7%) showed a mild chronic inflammatory infiltrate in the lamina propria and 95 (56.9%) of the cases exhibited vertically oriented, dilated capillaries (vascular ectasia) in the papillary lamina propria. Only three cases exhibited mild reactive epithelial atypia (Fig. 3e).

The study for p53 in 12 randomly selected cases showed low-intensity nuclear positivity in less than 25.0% of basal and parabasal cells and less than 5.0% positivity in five cases (Fig. 4a, Table 3). A similar expression pattern of p53 was observed in 10 cases of benign reactive/frictional keratosis of nonkeratinized sites (morsicatio mucosae oris) (Fig. 4b).

Discussion

BARK is a hyperkeratotic lesion caused by trauma or friction that occurs on the keratinized mucosa of the gingiva or alveolar ridge mucosa [1]. It is histopathologically similar to lichen simplex chronicus, a dermatological condition caused by repeated rubbing and scratching of the skin, mainly in

Table 2 Histopathologic features of benign alveolar ridge keratosis

Stratum corneum		
Orthokeratin		161 (96.4%)
Mild	46 (28.5%)	
Moderate	82 (51.0%)	
Severe	33 (20.5%)	
Parakeratin		45 (27.0%)
Partial	39 (23.4%)	
Complete	6 (3.6%)	
Bacterial colonies	15 (9.0%)	
Hypergranulosis		161 (96.4%)
Wedge-shaped	111 (69.0%)	
Epithelial surface configuration		
Corrugated	118 (70.6%)	
Flat	49 (29.4%)	
Epithelial thickness		
Mild acanthosis		151 (93.8%)
Moderate acanthosis		10 (6.2%)
Normal		6 (3.6%)
Atrophy		0 (0%)
Rete ridges		
Tapered	165 (98.8%)	
Interconnected	163 (97.6%)	
Bulbous	3 (1.8%)	
Chronic inflammatory infiltrate		53 (31.7%)
None to mild	50 (94.3%)	
Moderate	3 (5.7%)	
Vascular ectasia		95 (56.9%)
Ulceration		7 (4.2%)
Intraepithelial hemorrhage and/or subepithelial fibrin		
Others		
Odontogenic rest	11 (6.6%)	
Amalgam tattoo	5 (3%)	
Melanophages and melanin incontinence	4 (2.4%)	
Neural tissue hyperplasia	3 (1.8%)	
Reactive epithelial atypia	3 (1.8%)	
Foreign body/foreign body granuloma	2 (1.2%)	

the anogenital area and extremities [3]. BARK occurs in patients mainly in their 5th–8th decades with a male predilection (2:1), consistent with the reported age and gender predilection in a previous study [1]. Approximately 2/3 occur on the retromolar pad and 1/3 on the edentulous ridge mucosa. More than 1/3 of the cases had history of complete or partial edentulism. Bilateral lesions were reported in 29 cases (17.4%) which is similar to the previously reported prevalence (19%) [1]. However, it is not clear whether other lesions were also bilateral since this was not stated. Smoking status was likely the reason that prompted extra-vigilance and the biopsy as greater than 90% of patients where smoking status was known were biopsied.

More than 95% of BARK cases showed hyperkeratosis with two-thirds exhibiting a wedge-shaped pattern hypergranulosis. Focal parakeratosis was always associated with ulceration or bacterial colonization consistent with recent trauma to the area. Surface corrugation is common and should not be mistaken for atypical verrucous hyperplasia. To this point, two cases were diagnosed as papilloma clinically. Almost all cases showed acanthosis which is expected for a reactive lesion. On the other hand, no cases exhibited epithelial atrophy which would be inconsistent with a reaction to chronic irritation. Additionally, more than half of the cases showed vascular ectasia in the papillary lamina propria, a common finding in oral reactive keratotic lesions.

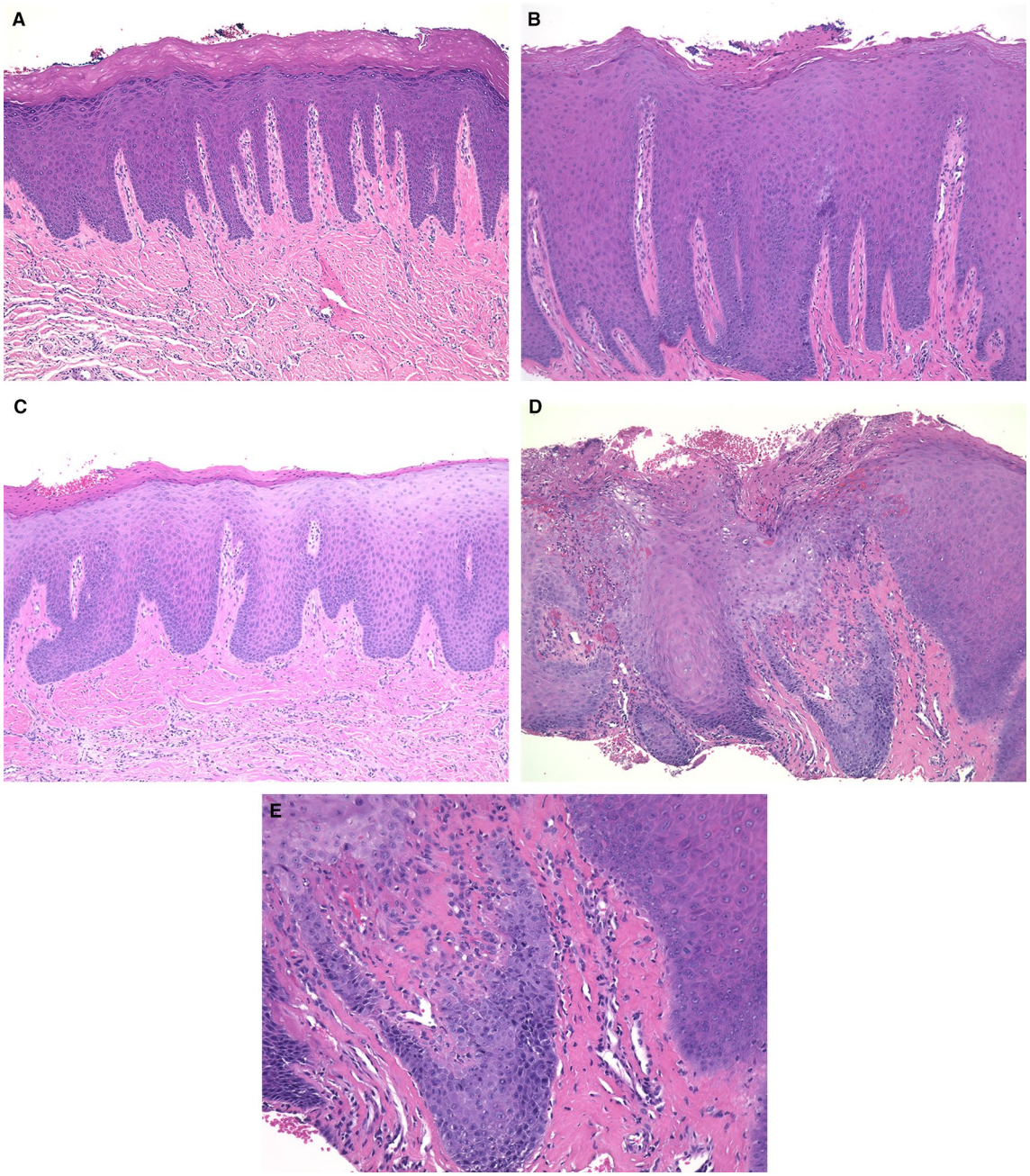

Fig. 3 **a** Histopathology of BARK: Corrugated hyperkeratosis, wedge-shaped hypergranulosis, acanthosis and tapered rete ridges (H&E, original magnification ×100). **b** Histopathology of BARK: Shaggy parakeratin with surface bacterial colonies, acanthosis with tapered rete ridges joined at the tips, and vascular ectasia (H&E, original magnification ×200). **c** Histopathology of BARK: Shaggy parakeratin which tapers to normal thickness at the edge, acanthosis and tapered rete ridges which are interconnected (H&E, original magnification ×100). **d** Histopathology of BARK: Shaggy parakeratosis, acanthosis with intraepithelial hemorrhage (arrows) and intra- and sub-epithelial fibrin deposition consistent with the edge of an ulcer (H&E, original magnification ×100). **e** Histopathology of BARK: Reactive epithelial atypia is evident associated with an ulcer edge (H&E, original magnification ×200)

A previously reported entity, alveolar ridge keratosis (ARK), was defined as any white patch or plaque without erythema or ulceration, limited to the retromolar pad or edentulous alveolar ridge mucosa [20, 21]. Although 2.1% (10 cases) of ARK cases exhibited dysplastic changes, the histopathologic features of the other 97.9% of cases were not specified other than that they were hyperkeratotic without dysplasia and we speculate that most of these likely represented BARK because frictional keratoses are by far, the most common keratotic lesions biopsied in the oral cavity

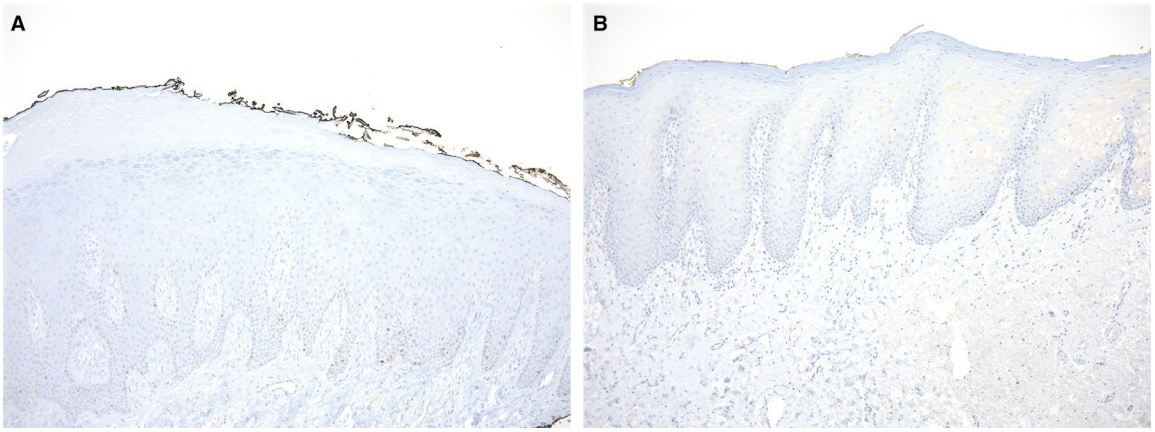

Fig. 4 **a** Nuclear positivity for p53 in less than 5% of basal cell nuclei in BARK (IHC, original magnification × 100). **b** Nuclear positivity in less than 5% of basal cell nuclei in morsicatio mucosae oris (IHC, original magnification × 100)

Table 3 Immunohistochemical study of p53

Percentage of positive cells	Benign alveolar ridge keratosis	Control (Morsicatio mucosae oris)
Percentage of positive cells (%)		
< 5	5 (41.7%)	6 (60%)
< 25	7 (58.3%)	4 (40%)
> 25	0	0
p53 expression pattern		
Basal cell layer	5 (41.7%)	5 (50%)
Basal/parabasal cell layer	7 (58.3%)	5 (50%)
Suprabasal cell layer	0	0
Intensity		
High	0	1 (10%)
Low	12 (100%)	9 (90%)

in the U.S. as noted in one study [7]. Dysplastic changes were associated with verrucous appearance, tobacco, alcohol, multiple leukoplakias or history of oral squamous cell carcinoma [20]. Hyperkeratotic lesions with epithelial atrophy (as opposed to acanthosis) with minimal inflammation (not BARK but would qualify for ARK) have been shown to harbor mutations at the same rate as moderate and severe epithelial dysplasia and are likely precancerous lesions when presenting clinically as demarcated plaques [22, 23]. An example of such a case of hyperkeratosis with epithelial atrophy is presented in (Fig. 5a–c).

Morsicatio mucosae oris which histopathologically exhibits parakeratosis and acanthosis with variable inflammation is well-recognized as a frictional/factitial keratoses that occurs on nonkeratinized sites such as the buccal mucosa, lateral/ventral tongue and lip mucosa. The masticatory mucosa of the gingiva is a first site of food impaction when chewing and as such, one would expect that such lesions are frequently encountered especially on the edentulous ridge without protection of teeth, or that is traumatized by a removal prosthesis. Clinicians see and biopsy such white lesions which form a substantial portion of any biopsy service, but which are generally diagnosed as "hyperkeratosis and acanthosis". BARK is just such a lesion and it is possible that its resemblance to lichen simplex chronicus is because it is located on keratinized tissue similar to skin.

Leukoplakia may occur anywhere in the mouth but differs from BARK in several ways. Clinically, leukoplakia is usually a demarcated plaque often with fissures (Fig. 5a), and is highly but not invariably associated with the dysplastic phenotype, while BARK is a poorly demarcated plaque with distinct histopathologic features similar to cutaneous lichen simplex chronicus, a reactive/frictional keratosis. Recognizing and referring to such reactive lesions specifically as BARK both clinically and histopathologically and not just "hyperkeratosis, no dysplasia", distinguish them from leukoplakias. Just as we would not diagnose biopsies of clinical lesions of morsicatio mucosae oris as "hyperkeratosis, no dysplasia", but more accurately as "chronic frictional/factitial keratosis" or "parakeratosis and acanthosis, reactive", it is not helpful to the clinician to diagnose lesions of BARK in that non-specific fashion. A diagnosis of hyperkeratosis not otherwise specified, defaults to a clinical diagnosis of leukoplakia.

Leukoplakia that histopathologically exhibits hyperkeratosis with epithelial atrophy or acanthosis but without the dysplastic phenotype, has been referred to conceptually as "keratosis of uncertain significance (KUS)" [7]. A more accurate and clinically useful diagnosis is "hyperkeratosis and epithelial atrophy (or acanthosis), not reactive" to connote that such lesions, unlike BARK, are not in reaction to local trauma or other inflammatory condition. Proliferative

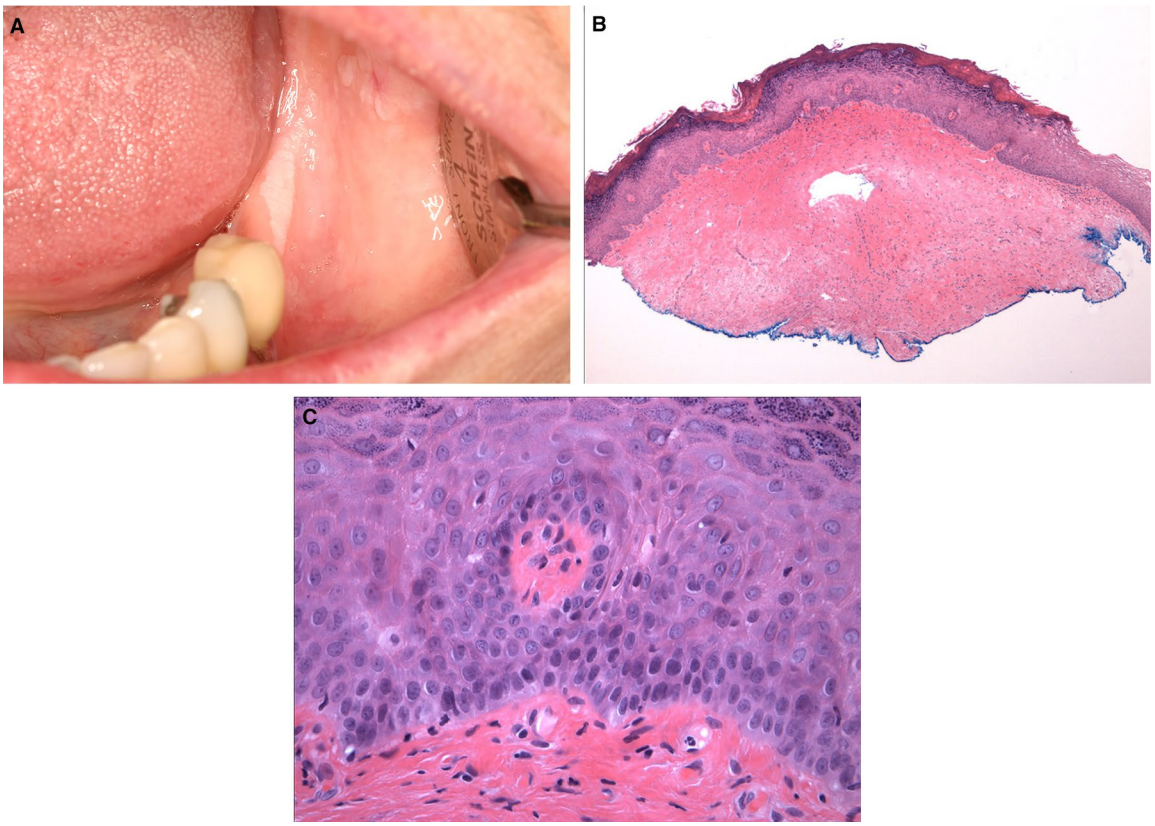

Fig. 5 **a** Leukoplakia on the retromolar pad. Note the sharply demarcated margin. **b** Histopathology of 5A: Hyperkeratosis, corrugated epithelial atrophy and poorly formed rete ridges (H&E, original magnification ×20). **c** Histopathology of 5A: Mild epithelial atypia, poorly formed rete ridges and no evidence of inflammation (H&E, ×400)

leukoplakia often presents as a KUS in early stages and yet 70–100% of these ultimately undergo malignant transformation [24, 25]; such cases also harbored similar mutations as those of moderate and severe dysplasia [23, 26] or other mutations [26]. Furthermore, many lesions of proliferative leukoplakia involve the gingiva and three cases in the study by Chi et al. [20] that exhibited dysplasia had multifocal disease and as such may have represented proliferative leukoplakia.

Wild-type p53 is tightly regulated and kept at low levels by p53 targeting ubiquitin ligase, MDM2 which degrades p53 [27]. As such, p53 expression is present in normal and reactive tissue with a pattern of scattered and faint positivity within basal cell nuclei. In the event of stress, the p53 protein degradation process is halted and p53 expression is stabilized resulting in increased p53 expression in oral epithelial dysplasia. p53 gain-of-function mutation in one allele causes genomic instability and promotes tumorigenesis regardless of the presence of wild-type p53 in the other allele. Mutated p53 binds to DNA and transcription factors resulting in altered gene expression, protein synthesis and cellular function leading to carcinogenesis [27]. Low p53 expression implies no significant underlying molecular stresses present in the tissue, similar to p53 phenotype we have seen in BARK. As such, BARK is a benign, reactive condition with no malignant potential.

A drawback of a retrospective study such as this that relies on community-based biopsies is the lack of follow-up. In other words, how do we know these are not early dysplastic leukoplakias in a few years, may transform to carcinoma? Several aspects of BARK support the benign nature of this condition. Firstly, even if one factors in patients who move to another part of the country or where a re-biopsy is seen by another service, we have not to-date seen a re-biopsy of a lesion previously diagnosed with BARK over the last 15 years (since we started using this term) that has transformed to carcinoma. Secondly, many of the lesions of BARK on the retromolar pad or edentulous ridge mucosa are bilateral, symmetric and poorly-demarcated, typical for reactive keratoses. Thirdly, the pattern of p53 expression supports a nondysplastic phenotype. After all, patients with frictional/factitial keratoses of morsicatio mucosae oris and accentuated linea alba are not followed for malignant transformation, and BARK falls into this similar category of frictional/factitial keratosis.

Conclusion

BARK is a specific clinical and pathologic entity that typically presents as a poorly demarcated plaque on the keratinized mucosa of the retromolar pad or edentulous alveolar ridge mucosa in elderly adults with a slight male predilection and has specific histopathology, similar to that cutaneous lichen simplex chronicus. BARK is likely caused by repeated frictional trauma from food or an ill-fitted prosthesis and has no malignant potential as supported by the pattern of low p53 expression. BARK is the clinical counterpart of morsicatio mucosae oris, another frictional keratosis which is located on the nonkeratinized mucosae of the buccal mucosa, tongue and lip mucosa.

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Compliance with Ethical Standards

Conflict of interest No conflict of interest to disclose.

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