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Proliferative verrucous leukoplakia and its progression to oral carcinoma: a review of the literature

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BACKGROUND: Proliferative verrucous leukoplakia (PVL) is a distinct clinical form of oral leukoplakia defined by its progressive clinical course, changing clinical and histopathological features, and potential to develop into cancer. PVL behaves in a more aggressive and relentless manner than the more innocuous white oral lesions that it can resemble clinically.

METHODS: A PubMed search was conducted which identified studies that examined patients with PVL and reported data meeting inclusion criteria.

RESULTS: PVL is seen much more frequently in females and most often diagnosed after the sixth decade of life. Tobacco use is not strongly linked to the presence of PVL (63% of patients did not use tobacco products). Most (74%) of the patients with PVL progressed to oral carcinoma.

CONCLUSION: PVL is a persistent and progressive oral lesion that requires very close follow-up along with early and aggressive treatment to increase the chances of a favorable outcome.

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Keywords: proliferative verrucous leukoplakia; oral cancer; squamous cell carcinoma; verrucous carcinoma

Introduction

Oral leukoplakia is a clinical descriptive term for predominantly white lesions of the oral mucosa that cannot be removed by scraping and cannot be classified clinically or diagnostically as any other disease entity. It is not a histologically appropriate diagnostic term for any one pathological entity. Shear and Pindborg coined the term verrucous hyperplasia of the oral mucosa in 1980. In their review of 68 cases, they found more cases in women, the majority of whom were over 50 years of age (35% over 70 years of age). Histological dysplasia was reported in 66%, verrucous carcinoma (VC) in 29%, and squamous cell carcinoma (SCC) in 10% (1). In their 1984 study of 257 patients, Silverman *et al*. documented a high rate of malignant transformation in a subset of study patients with verrucous leukoplakia (2). In 1985, Hansen *et al*. further characterized this type of lesion and assigned it the term proliferative verrucous leukoplakia (PVL) (3). It is important to note that PVL is a clinical diagnosis for leukoplakias that encompass a spectrum of clinical and histopathological stages prone to exhibit recurrence and, at times, the clinical and microscopic features of malignancy. Several studies have examined the long-term characteristics of PVL and its propensity to develop into carcinoma. Some interesting trends describing the presentation and progression of PVL are revealed in those studies. The purpose of this review was to evaluate published data that examined PVL and its progression to carcinoma and to discuss the clinical, histopathological, pathogenic, and cellular characteristics of PVL along with possible management strategies.

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Methods

A PubMed search was conducted using PVL as a search term. Additional references were included based upon the original literature search and references used in the selected papers. To qualify for inclusion, studies had to present information regarding patient demographics, tobacco use, diagnosis, and follow-up. The clinical and histological criteria included persistent or progressive white, granular, or verrucous oral leukoplakia with or without histological evidence of dysplasia or carcinoma.

Results

In addition to the three PVL cases we reported (4), cases from five additional studies (3, 5–8) met our inclusion criteria (Table 1). Bagan *et al*. studied 30 PVL patients

Table 1 Studies examining PVL and its progression to carcinoma

Study	Patients with PVL				Patients progressing to carcinoma	Mean length of follow-up (years)
	Male	Female	Tobacco users	Mean age at diagnosis (years)		
Morton *et al.* (4)	1	2	1	80	3 (100%)	3.7
Bagan *et al.* (5)	6	24	7	71	19 (63%)	4.7
Fettig *et al.* (6)	6	4	3	65	6 (60%)	4.4
Silverman and Gorsky (7)	11	43	17	62	38 (70%)	11.6
Zakrzewska *et al.* (8)	5	5	5	64	10 (100%)	6.6
Hansen *et al.* (3)	6	24	18	66	26 (87%)	6.1

PVL, proliferative verrucous leukoplakia.

(six male, 24 female, seven tobacco users) with a mean age at PVL diagnosis of 71 years. Nineteen of the 30 patients (63%) showed progression of PVL to carcinoma over a mean follow-up of 4.7 years (5). Fettig *et al.* examined 10 PVL patients (six male, four female, three tobacco users) with a mean age at PVL diagnosis of 65 years. Six of the 10 patients (60%) exhibited progression of PVL to carcinoma over a mean follow-up period of 4.4 years (6). Silverman and Gorsky studied 54 PVL patients (11 male, 43 female, 17 tobacco users) with a mean age at PVL diagnosis of 62 years. Thirty-eight of the 54 patients (70%) showed progression of PVL to carcinoma over a mean follow-up period of 11.6 years (7). Zakrzewska *et al.* examined 10 PVL patients (five male, five female, five tobacco users) with a mean age at PVL diagnosis of 64 years. All of the 10 patients exhibited progression of PVL to carcinoma over a mean follow-up period of 6.6 years (8). Hansen *et al.* studied 30 PVL patients (six male, 24 female, 18 tobacco users) with a mean age at PVL diagnosis of 66 years. Twenty-six of the 30 patients (87%) showed progression of PVL to carcinoma over a mean follow-up period of 6.1 years (3).

The pooled data from the 137 patients in the eligible studies were summarized (Table 2). One hundred two patients were female (74%). Fifty-one of the patients smoked and/or chewed tobacco (37%). The mean age at diagnosis of PVL in the studies ranged from 62 to 80 years, with a grand mean of 66 years. The intrastudy percentages of PVL patients progressing to oral carcinoma ranged from 60% to 100%. One hundred two patients experienced progression of PVL to VC or SCC (74%). The mean length of follow-up in the studies ranged from 3.7 to 11.6 years, with a grand mean of 7.8 years.

Table 2 Review of studies examining PVL and its progression to carcinoma

Total number of patients with PVL	137
Male	35 (26%)
Female	102 (74%)
Total number of tobacco users	51 (37%)
Grand mean age at diagnosis (years)	66
Total number of patients progressing to carcinoma	102 (74%)
Grand mean length of follow-up (years)	7.8

PVL, proliferative verrucous leukoplakia.

Discussion

Clinical characteristics

The clinical presentation and lesion behavior are important in the diagnosis of PVL. One of the hallmarks of PVL is its variable and progressive clinical presentation. PVL may appear on any soft tissue surface of the oral cavity and may present as a single distinct lesion or, less often, as scattered multifocal growths involving several oral sites. A case of PVL with cutaneous involvement has also been reported (9). The buccal mucosa and tongue are the most common sites associated with PVL, with palatal mucosa, alveolar mucosa, gingiva, floor of mouth, and lip showing a lower incidence (3, 10). PVL most often manifests as a flat white keratotic lesion with a grainy or verrucous surface. As such, this lesion is not readily distinguishable from more innocuous forms of leukoplakia or from verrucous lesions due to other causes. In some cases, there is an erythematous component. As the lesion progresses, it may exhibit horizontal and vertical growth, eventually taking on a more exophytic granular or verruciform appearance. PVL is notoriously slow growing and recurs following treatment, continuing in its relentless progression. It can display a variety of clinical and histopathological features, progressing into diffuse, wart-like intraoral lesions that may be erythematous and erosive. PVL may progress to multiple oral foci of VC or SCC over time in spite of numerous treatment interventions, suggesting that PVL is associated with diffuse submicroscopic changes of the oral mucosa, sometimes described as 'field cancerization' (11, 12).

Histopathobiological characteristics

The progressive epithelial changes associated with PVL make the initial microscopic diagnosis of this lesion difficult. Frequently, a pathological diagnosis of benign cellular or minimal dysplastic changes is made, while the clinically aggressive behavior of the lesion is more consistent with a diagnosis of carcinoma. Hansen *et al.* proposed microscopic grading of PVL on a scale from 0 to 10 denoting a continuum of severity that included histologically normal oral mucosa, clinically homogenous leukoplakia, verrucous hyperplasia, VC, papillary SCC, less-differentiated SCC, and intermediates (3). Batsakis *et al.* suggested a histological staging of PVL that included four phases (clinically flat leukoplakia

without dysplasia, verrucous hyperplasia, VC, and conventional SCC) with intermediates (10). The above PVL classification methods differ mostly on their interpretation of what lesions fit into a diagnosis of papillary SCC. The Batsakis *et al*. staging criteria include in the VC grouping lesions described as papillary SCC under the Hansen *et al*. classification system. Furthermore, Batsakis *et al*. describe histological similarities between verrucous hyperplasia and VC that makes distinguishing between them difficult. Shear and Pindborg were the first to describe this mucosal condition and coined the term 'verrucous hyperplasia' (1). Some authors regard verrucous hyperplasia to be a morphological variant of VC. Others consider verrucous hyperplasia to be an irreversible precursor of VC and recommend that both lesions be managed in the same manner (10). It is apparent that precise classification of PVL in a staging continuum is problematic because sampling of the lesions occurs at uncontrolled intervals and because of the minimal cellular atypia often seen on biopsy. Grouping lesions with similar histopathological features may help provide a prognostic pattern of a lesion's progression based upon the general histomorphological and specific cytological changes within the epithelium of the lesion and the temporal proximity of these features to the clinicobiological behavior of a carcinoma.

Proliferative verrucous leukoplakia exhibits progressive histopathological features that may be observed in a single biopsy, multiple biopsies taken from a patient at the same time, or serial biopsies taken over time. Often, an interface lymphocytic infiltrate is present within the superficial lamina propria that is similar to and often mistaken for lichen planus. The lymphocytic infiltrate may be intense and obscure visualization of the basement membrane (Fig. 1). Apoptotic cells and eosinophilic ovoid (Civatte, colloid, cytoid, hyaline) bodies may occasionally be identified. With time, there may be corresponding histopathological findings of increased keratosis with an increasingly corrugated or verruciform surface (Fig. 2). Enhanced acanthosis and basilar

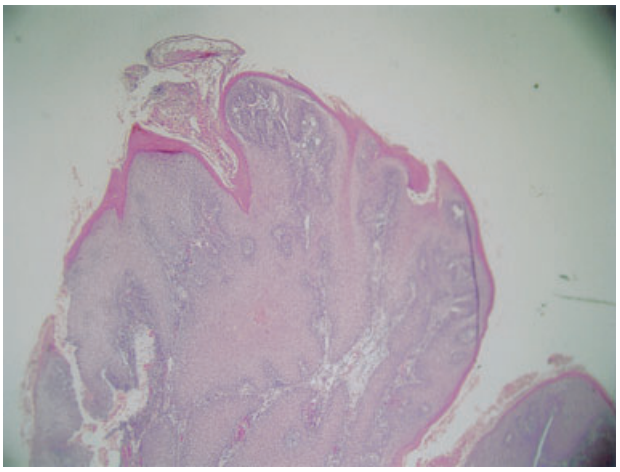

Figure 2 Verruciform epithelial hyperplasia (hematoxylin and eosin stain, ×40).

hyperplasia with or without dysplasia may be identified. Frequently, there is an abrupt transition from hyperparakeratosis to hyperorthokeratosis (Fig. 3).

The progressive histological features of PVL may include features that are mistaken for lichen planus or associated with areas that are or have been diagnosed as lichen planus (13, 14). A stage of PVL must be considered in cases of lichenoid interface inflammation with basilar hyperplasia and hyperkeratosis without evidence of basilar vaculopathy. In advanced cases, the deeply folded tissue may erode and infiltrate the underlying bone-forming pseudocysts that may be mistaken for odontogenic cysts (Fig. 4). If the lesions continue to grow horizontally and vertically, there are concurrent histopathological changes of increasing hyperkeratosis with increased surface folding, verrucous papillomatosis, acanthosis, and basilar hyperplasia with or without dysplasia. Only if these latter histopathological changes are observed and/or there is recurrence of a previously excised lesion could a white lesion be considered consistent with PVL clinically. If lesions

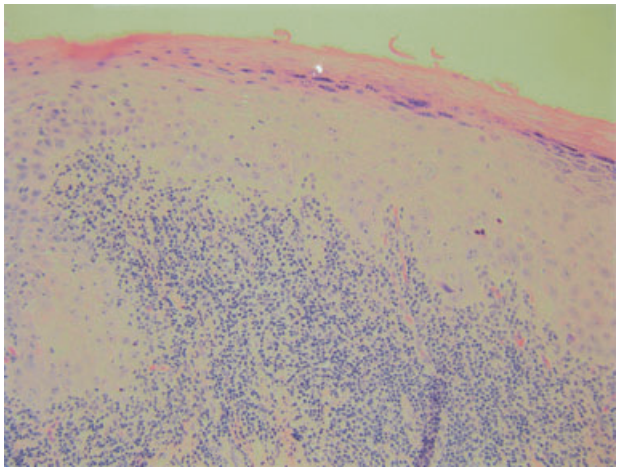

Figure 1 Lichenoid lymphocytic infiltrate (hematoxylin and eosin stain, ×200).

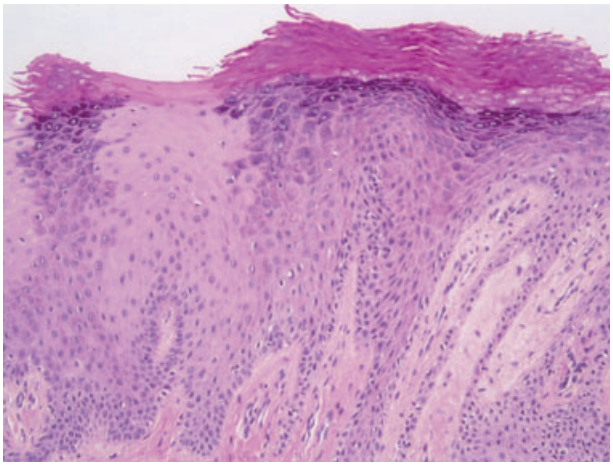

Figure 3 Abrupt transition from hyperparakeratosis to hyperorthokeratosis (hematoxylin and eosin stain, ×200).

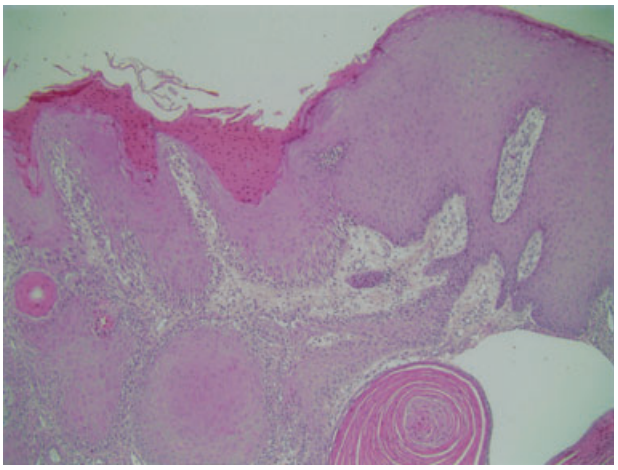

Figure 4 Pseudocystic structures (hematoxylin and eosin stain, ×100).

with the clinical and histological features of PVL are not aggressively treated, they will recur and may progress to VC and/or SCC (Fig. 5).

The pathoetiology of PVL is an area of continuing debate. Various studies have examined viral, fungal, genetic, and immunological influences on the pathogenesis and behavior of PVL. Palefsky *et al.* found that of nine PVL lesions from seven patients, eight of the lesions were positive for human papillomavirus (HPV) by polymerase chain reaction (PCR) for HPV DNA, with seven of them positive for oncogenic HPV-16. The control group of non-PVL-associated oral lesions, including some SCCs, yielded a smaller percentage of HPV positivity (15).

Gopalakrishnan *et al.* examined the frequencies of overexpression and mutation in the p53 tumor suppressor gene in PVL and oral SCC employing immunohistochemistry and PCR amplification. In their study, 10 samples each of normal oral mucosa, PVL, and SCC were immunostained with antibodies against p53 protein. Eight of 10 cases of PVL and seven of 10 cases of oral SCC were positive for p53 protein. Minimal staining was observed in normal oral tissues. Single-strand conformation polymorphism analysis demonstrated p53 gene mutations within exons in four of 10 of the SCC samples. However, two of the four mutated SCC samples lacked p53 expression. No p53 mutations were detected in the PVL lesions (16).

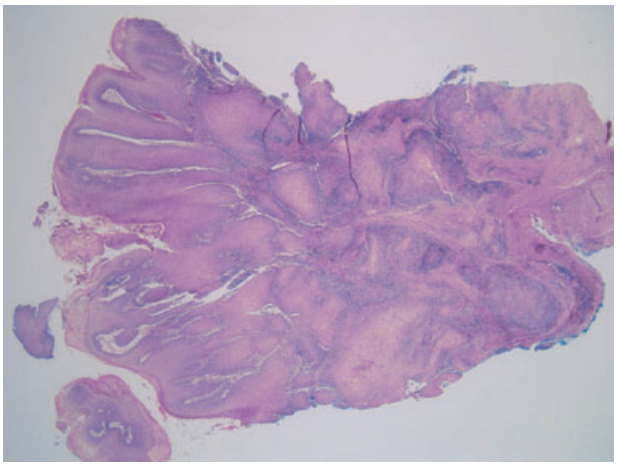

Figure 5 Squamous cell carcinoma arising in proliferative verrucous leukoplakia (hematoxylin and eosin stain, ×40).

This study also compared the presence of HPV and p53 in SCC and PVL. HPV-16 was identified in two of seven p53-positive oral SCC lesions, while HPV-16 and -18 were identified in two of eight p53-positive PVL lesions. A single p53-negative SCC sample was HPV-16 positive and had a mutation in an exon of the p53 gene (16). Fettig *et al.* examined 10 cases of gingival PVL by evaluating p53 expression immunohistochemically and determining the presence of HPV DNA with PCR amplification. Positive p53 staining was evident in four of the 10 cases; HPV was not detected in any of the lesions (6). Thus, it appears that HPV may be present in some, but not all, lesions of PVL.

Patterns of immunoreactivity in PVL and SCC displaying similar characteristics of mitogenic transforming growth factor alpha (TGF-α) are suggestive of an evolutionary link between those lesions (17, 18). Kannan *et al.* examined the expression of TGF-α in PVL, oral SCC, and normal mucosa. Immunohistochemical localization of TGF-α in archival paraffin-embedded sections of 10 cases each of PVL, oral SCC, and normal oral mucosa was performed with commercially available monoclonal antibodies. The study demonstrated that increased TGF-α immunoreactivity occurred in PVL and oral SCC sections relative to normal controls (18).

DNA ploidy has been studied as a possible indicator of disease stage and clinical outcome in oral leukoplakia (19, 20), but some study results have been controversial (21). Kahn *et al.* examined four cases of PVL to determine if flow cytometry could be useful in the early diagnosis of PVL. Flow cytometric analysis was performed on formalin-fixed paraffin-embedded specimens and showed DNA aneuploid cell lines in each PVL case studied (19).

A link between the upregulation of cyclooxygenase-2 (COX-2) expression and oral pre-malignancy has been proposed (22–26), which may have implications in diagnosis and possible future studies of management of oral leukoplakia including PVL. COX-2 is expressed as an early response to growth factors as well as tumor promoters and other carcinogens (22). COX-2 overexpression may play a role in upper aerodigestive tract cancer by leading to an increased cell proliferation, reduced apoptosis, prolonged survival of cells containing damaged DNA, enhanced cell invasion, and increased vascular permeability (22). Chan *et al.* found that mean levels of COX-2 mRNA were increased by nearly 150-fold in 24 patients with head and neck SCC compared with normal oral mucosa from 17 healthy volunteers. Additionally, there was about a 50-fold increase in amounts of COX-2 mRNA in normal-appearing epithelium adjacent to areas of 10 cases of head and neck SCC compared with normal oral mucosa from healthy volunteers. Immunoblotting demonstrated

that COX-2 protein was present in six of six cases of head and neck SCC but was undetectable in normal oral mucosa from healthy subjects (23). Mestre *et al*. examined levels of COX-2 mRNA in 15 cases of head and neck SCC and 10 cases of normal oral mucosa. Nearly a 100-fold increase in amounts of COX-2 mRNA was detected in head and neck SCC (24). Sudbø *et al*. compared levels of COX-2 expression in healthy, pre-malignant, and cancerous oral mucosa (25), and despite a positive report, the utility of COX-2 inhibitors in management of oral leukoplakia remains unclear.

The lack of reliable diagnostic and prognostic markers for PVL (26, 27) has led several studies to focus on evaluating tumor suppressor loci for loss of heterozygosity (LOH) (28–33). Epstein *et al*. obtained 39 toluidine blue positive biopsy specimens of oral pre-malignant lesions from 32 patients and analyzed the specimens for LOH at 10 microsatellite loci on three chromosome arms (3p, 9p, and 17p). Of the 39 specimens, 29 showed LOH (28). Partridge *et al*. screened 48 primary oral SCCs for allelic imbalance at 19 loci often mutated in head and neck SCC. Allelic imbalance was detected at all TNM stages with stage 4 tumors showing significantly more aberrations than stage 1–3 tumors. The hazard ratios for survival analysis revealed that patients with allelic imbalance at 3p24-26, 3p13, and 9p21 had a 25-fold increase in their mortality rate relative to a patient retaining heterozygosity at these loci (32). Jiang *et al*. investigated LOH in 13 cases of oral leukoplakia with foci of early cancer within the lesions. LOH detected in the leukoplakia was identical to that observed in the foci of early cancer within the leukoplakia in 11 of 13 cases. Two of the cases showed allelic imbalance (33).

Tobacco use has not been directly associated with PVL. In our meta-analysis, 37% of patients with PVL reported a history of tobacco use. No correlation has been shown in the literature between the presence of an immunodeficiency and PVL. There is some evidence of increased risk for PVL-associated histological changes in patients with long-standing graft-versus-host disease (10, 14, 34).

Management and outcomes

Because of the relentless growth pattern associated with PVL and its propensity to develop into carcinoma (3–8, 35–37), early and aggressive treatment of such a lesion is recommended (6, 7, 11). PVL frequently appears as an innocuous white patch that can be overlooked or interpreted to be a lesion of little significance. The histopathological evaluation of a lesion falling into the PVL disease continuum of variants can vary widely based on who is providing the diagnosis and that diagnostician's interpretation of a variant's histological pattern (38, 39). Diagnosis can be further complicated by the fact that dysplastic changes may be minimal despite aggressive behavior of the lesion. Therefore, clinical behavior must be carefully assessed to guide treatment.

Surgical treatment of PVL is accomplished via scalpel or laser excision. However, recurrence of PVL following surgical removal is not unusual. Femiano *et al*. compared surgery in 25 HPV-positive PVL patients with combined therapy using surgery and methisoprinol (isoprinosine or inosine pranobex), a synthetic agent with immunomodulatory properties and potential antiviral activity against HPV, in another group of 25 patients with PVL. Eighteen months postoperatively, there was a significant difference, with 18 recurrences in the patients treated by surgery alone compared with four recurrences in the patients treated with surgery and methisoprinol (40). Schoelch *et al*. studied 70 consecutive laser-treated patients with oral leukoplakia, 12 of whom had PVL lesions followed for 6 months or longer. Ten of the 12 PVL patients had recurrent lesions (83%), nine of whom had lesions that were eventually controlled with subsequent laser surgeries. Two of the PVL patients developed carcinoma (41). Non-surgical therapeutic approaches for PVL have been considered, such as external beam radiation therapy, cryotherapy, and topical vitamin therapy, but none has proven to be beneficial (7, 10). Early trials of topical chemotherapy with bleomycin have been assessed (42, 43). Surgical shave followed by cryosurgery (44) and photodynamic therapy (45, 46) have also been suggested. In the future, anti-HPV, anti-TGF, and pro-apoptotic management strategies may be considered. The challenge is to administer sufficiently aggressive therapy consistent with clinical progression of the lesion despite the often benign histological findings. Currently, poor outcomes with a high risk of progression to cancer may be reflective of undertreatment and the lack of effective therapies for PVL. If molecular markers of PVL and an associated risk of progression to cancer are found, the identification of more effective therapies than those presently available may be facilitated.

Conclusion

This analysis of published cases shows that PVL is seen much more frequently in females than males and is typically diagnosed after the sixth decade of life. These studies indicate that tobacco use is not strongly linked to the presence of PVL, as 63% of the PVL patients studied did not use tobacco products. Furthermore, this analysis suggests that a high percentage of PVL lesions progress to oral carcinoma over time in spite of a variety of interventions. This characteristic contrasts with the widely held view that approximately 5% of all leukoplakias will transform into a carcinoma within about 5 years (47). Clearly, PVL is a persistent and progressive oral lesion that requires early and aggressive treatment to increase the chances of a favorable outcome. In addition, the implementation of improved diagnostic and therapeutic approaches is needed to aid in the management of PVL.

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