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Title Page:
Management of Proliferative Verrucous Leukoplakia: Justification for a Conservative Approach.

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Running title: Management of PVL
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Abstract

Background

Proliferative verrucous leukoplakia (PVL) is a progressive, multifocal, exophytic

form of leukoplakia with high rates of malignant transformation.   The aim of

this study is to evaluate a cohort of PVL in a single tertiary referral clinic.

Method

Cases meeting accepted diagnostic criteria were reviewed with regard to their

pathology, demographic characteristics, management & outcomes. HPV testing

was undertaken on a subset, all of which were negative.

Results

Almost half of the 48 patients with PVL (48%, n=23) underwent malignant

transformation after a median 23.4 months. The characteristics of this cohort

were similar to those previously described, but management was notably more

conservative. Conservative management of PVL was used in 92% of our patients,

but the clinical outcomes appear comparable to previously described cohorts

where PVL was predominantly treated by surgical excision.

Conclusions

Aggressive surgical intervention in the premalignant phase of PVL may not

influence the rate of malignant transformation.

Introduction.

Proliferative verrucous leukoplakia (PVL) refers to a distinct but rare subset of

oral leukoplakia. It is characterized by progressive, multifocal, exophytic lesions

that are persistent, irreversible and more common in elderly women without

risk factors[1-3]. Although only characterized in 1985[2], considerable attention

has been paid to PVL because of high rates of recurrence, malignant

transformation and mortality[1-3]. However, controversy persists regarding

diagnosis, aetiology and appropriate management.

The diagnosis of PVL cannot be established on histopathological findings alone

and requires correlation with a characteristic clinical appearance of progressive

demarcated florid white lesions[4] (Figure 1). Major and minor diagnostic criteria

based on both clinical and histopathological features have been suggested[5] and

variously endorsed[6]. In their original account, Hansen et al[2] described a 10-

point histological grading from 0 (normal) to 10 (frankly invasive squamous cell

carcinoma), although a simplified scheme with 4 histopathological sub-types[4]

has been published. It is accepted that some temporal progression in the clinical

and pathological features is required before a diagnosis of PVL, implying,

therefore, the need for retrospective review[7]. The differential diagnosis from

other conditions has been described[8].

The aetiology of PVL remains obscure, with no recognized risk factors other than

advanced age and female gender. Although some early reports suggested a link

between oncogenic viruses and PVL[3, 9], recent reports have not demonstrated

an association with either high risk Human Papillomavirus (HPV) sub-types or

Epstein-Barr Virus[10-12].

Owing to its progressive clinical course and tendency for malignant

transformation, PVL has generally been aggressively managed. In a recent

systematic review of 126 cases in which management was reported, surgery was

used in 80%, radiotherapy in 24%, laser excision or ablation in 23% and other

treatment methods in a further 12%[7]. Most patients received multiple

modalities and only 1.6% received no treatment, while 2.1% were managed

conservatively with regular monitoring and multiple biopsies. The aim of the

present study is to undertake a retrospective evaluation of patients diagnosed

with PVL in a multi-discipliary oral dysplasia clinic serving as a tertiary regional

referral centre. The demographic, clinical, histopathological characteristics,

management and clinical outcomes of PVL are compared with previous

published cohorts. The HPV status was also established on a sub-set of this

cohort.

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Materials & Methods

An evaluation of patients diagnosed with PVL in a regional referral centre for the period 1990-2015 was undertaken. Protocols for accepting new referrals, review and management of such lesions in this tertiary referral clinic have become increasingly formalised over the period[13-15]. Diagnostic criteria for and classification of PVL closely adhered to Hansen et al[2]. The histopathology for all cases was re-examined, with grades 3-5 usually considered to meet the histological requirement for an initial diagnosis of PVL. After defining the index lesion and date of diagnosis, ongoing management including biopsy, further management including surgery, malignant transformation and death were recorded and assessed using Kaplan Meier (KM) analysis, and Mann-Whitney or Fisher's exact testing. Tobacco and alcohol exposure were recorded in keeping with our previous reports of premaligant lesions[15], whereby smoking status was dichotomized as greater than 5 pack years, and alcohol user was greater than 5 units per week long term use.

Determination of HPV status was undertaken for a subset of PVL cases for which formalin-fixed paraffin-embedded (FFPE) tissue blocks were retrieved. Data and tissue were collected under ethical approval (South Sefton Research Ethics Committee; EC47.01 and North West 5 Research Ethics Committee; 09/H1010/54). Tissue microarrays (TMAs) consisting of triplicate cores of representative PVL tissue from corresponding FFPE tumour donor blocks were constructed according to standard protocols. HPV detection was based on combined assessment of p16 immunohistochemistry (IHC) and high risk HPV

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DNA in situ hybridisation (HR HPV DNA ISH). A sample testing positive for both

would confirm evidence of presence of HPV DNA and the downstream effects of

viral oncogene expression (p16 overexpression). Both p16 IHC and HR-HPV DNA

ISH analysis was conducted using proprietary kits (CINtec Histology, mtm

laboratories AG, Heidelberg, Germany; Inform HPV III Family 16 Probe B,

Ventana Medical Systems Inc., Tucson, AZ, USA) on a Ventana Benchmark

Autostainer (Ventana Medical Systems Inc.) as previously described[16]. Scoring

of p16 IHC status was assessed using the widely used threshold of strong and

diffuse nuclear and cytoplasmic staining in greater than 70% of the tumour cells.

HR HPV DNA ISH was scored using a binary classification (positive or negative)

reflecting detection of chromogen in any of the malignant cells, as previously

described[17].

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Results

Following assessment of clinical and histopathological characteristics, 48

patients were diagnosed with PVL. The characteristics of histopathology at the

first available biopsy are shown in Table 1. A typical illustrative case showing

many of the major and minor criteria for diagnosis of PVL is shown in figures

1,2,3 & 4.

77% (n=37) of patients presented with Hansen grades 3-5 on initial biopsy;

23%(n=11) of the cohort at both ends of the grading spectrum did not show

features in keeping with the histopathology of conventional PVL at presentation.

All patients were reviewed with a median follow up of 3.4 years (IQR 1.2-6.0

years) since diagnosis. The grading at the most recent available biopsy is also

shown in Table 1.

The demographic characteristics of patients and lesions were compared to the

Bagan and Silverman cohorts[1, 3] and are shown in Table 2, although some of the

comparisons were limited by differing methodology e.g. history of tobacco and

alcohol exposure was reported differently in the 3 cohorts.

In the current cohort, the site of lesions was pan-oral or multiple oral sites in

42% (20), gingivae in 33% (16), tongue only 13% (6), buccal only 8% (4) and

other 4% (2). Half (24) of patients were male. The largest total area of

leukoplakia was measured for 46 patients at: >=1000mm^2 (20%, 9 patients),

>=500-999mm^2 (30%, 14 patients), >=250-499mm^2 (20%, 9 patients) and

<250mm^2 (30%, 14 patients).

Active surveillance and repeat biopsy in the event of clinical change in appearance, were the most common method of management, used in 29 (60%) cases. Surgical excision of premalignant lesions (Hansen Grade 3-5) was performed in only 4 (8%) of patients, with 2 of those patients requiring marginal mandibular ('rim') resections and significant accompanying loss of dentition.

Almost half (23, 48%) underwent malignant transformation and the median follow up in those transformed was 8.2 years (IQR (interquartile range) 4.6-14.5) and in those not transformed 3.5 years (IQR 1.2-9.7) (Figure 5). Adjusting for variable follow-up using Kaplan-Meier survival (Figure 2) the 5-year estimate of transformation was 4% (SE 4%) and the 10-year estimate was 22% (SE 12%). The median time to transformation (time from PVL on initial biopsy to eventual, frankly invasive histology) was 23.4 months(IQR 0.4-55.0), n=23, and these patients had a median of 1 (IQR 1-3, range1-9) total number of diagnosed malignancies during their follow-up . A total of 6 (13%) patients died as a result of oral malignancy evolving from PVL.

Comparing the 23 patients who underwent malignant transformation with the 25 who did not; neither age, gender, smoking status, or alcohol consumption were statistically diffzerent between the groups (Table 3). The larger lesions of PVL and pan-oral sites were stastically more likley to undergo malignant transformation. Gingival only lesions were stasticalt more likely not to progress to malignancy . There was a confounding association with pan-oral PVL patients having larger lesions (14/20 with ≥500mm^2) than single site lesions, such as

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gingival only (9/16 with <250mm^2). Patients who underwent malignant

transformation received significantly more biopsies than those who did not

(median of 5 versus 1). 83% (19/23) of transformed patients, all with multiple

biopsies, showed a histological progression in grading.

15 of 48 had adequate tissue for HPV testing. All 15 patients tested for HPV were

negative in all tests.

Discussion

A notable finding of this retrospective study was that in our largely
conservatively managed (92%) cohort of patients with PVL there were similar
malignant transformation rates (48%) and fewer disease related deaths (12.5%),
when compared to the literature[1, 3, 7]. Large (>500mm2), pan-oral lesions,
present for a long duration of time (>8 years) were more likely to transform. It is
also evident that the clinical progress of these lesions to malignancy appears
slow and inexorable, therefore the true impact of the disease is only apparent
after prolonged longitudinal follow-up.

The inclusion criteria applied here, allowed only patients treated within a
specialist tertiary referral clinic, with confirmed clinical and histopathological
features of PVL, to enter the study. The weaknesses of our data, in common with
other published cohorts, lies in modest size and retrospective nature. Compared
with the other cohorts in the published literature (Bagan[1], Silverman[3]), our's has
shorter follow-up which might partly explain why the rate of malignant
transformation is broadly similar but mortality is significantly lower.

The demographics of our cohort are comparable to the literature, i.e. PVL mainly
affecting elderly patients and apparently with little contribution from
environmental carcinogens such tobacco or alcohol. Our findings also support
the lack of an aetiologiocal association between PVL and oncogenic HPV[10, 12].
We observed an equal representation of both males and females in our cohort,
which contrasts with the commonly reported female predominance [7]. We found

no association between gender and malignant transformation or death. Gingivae

are regarded as the most common site of PVL [7], but our findings indicate

multifocal disease (42% of patients) is more prominent than single site

presentation. Our cohort shows overall similar transformation rate and

histological progression of PVL as previously described[1-3].

We re-emphasise the lack of evidence to support the routine excision of the non-

invasive phase of PVL (Hansen grades 3-5) in an attempt to prevent future

malignant transformation. Our conservatively managed cohort is thus unique,

and our data questions the inference from other published series, i.e. that

empirical excision of PVL on presentation influences malignant transformation

or survival. We would stress the need for careful and lifelong surveillance of

patients with PVL in the context of a dedicated multidisciplinary team. Our aim is

to diagnose emergent malignancies as early as possible and offer standard

therapy based on the clinical staging of the emergent squamous cell carcinoma.

The certainty behind any recommendation is currently weak, and we

acknowledge the paucity of high quality data to inform treatment decisions for

PVL. However, the morbidity of surgical manipulations of PVL is sometimes

considerable, particularly the accumulated effects of repeat surgery. If this is

carried out without sufficient evidence of benefit, it might reasonably be open to

question. We have experienced that adequate excision of widespread gingival

lesions often requires loss of alveolar process and many or all teeth. Bearing in

mind that this group of patients have the lowest risk of malignant transformation

of all PVL sites, we find it particularly difficult to recommend this intervention.

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There is a need for greater awareness in the medical and dental communities of the existence of PVL and the importance of specialist management. Histopathological grading on first biopsy cannot be used in isolation to safely direct management, and clinical factors such as the appearance of the lesion and temporal trends are also crucial. In view of the relative rarity of PVL, multi-centre collaborative studies are required to better evaluate diagnosis and management, and establish more meaningful diagnostic and treatment guidelines for clinicians. Furthermore, the high transformation rates of PVL, suggest a role of as yet uncharacterized molecular aberrations. With the aid of modern genomic platforms, it may be now be possible to identify the critical aetiological events that underly the pathogenesis of this clinicopathologically challenging condition.

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FIGURE 1: Illustrative case of PVL. 79 year old female patient with longstanding history of PVL subject to two previous resections over 15 years for verrucous carcinoma (PVL grade 8). Presents with pan-oral lesions involving the mandulabar gingivae, with limited involvement of maxilla.

FIGURE 2: A more significant lesion involves the floor of mouth and ventral tongue. Excision of this revealed verrucous carcinoma resected with narrow margins; the patient remains under close clinical review.

FIGURE 3 Scanned histological sections of the excised lesion shown in Figure 2, stained with hematoxylin and eosin. The limited extent of the excision can be appreciated.

FIGURE 4 Areas of the sections shown in Figure 2 are magnified to illustrate the varying surface and front of PVL. (Unless otherwise specified, the photomicrographs were taken at a ×2 objective magnification.) (A) Compact, verrucous hyperorthokeratosis on the surface. (B) Finger-like exophytic papillary projections capped by hyperorthokeratosis, with 'shouldering' at the base. (C) Exophytic mammillated projection with inconspicuous keratinisation on the surface. (D) Focally infolded / invaginated surface. (E) Composite photomicrograph showing columns (arrow) and elephant feet-like arrangements (open arrow) of proliferative keratinocytes, which advance at more or less the same level; variable 'lichenoid' inflammatory reaction is sub-adjacent to the advancing front. (F) Gently mammillated surface, and front advancing at different levels, .though not extending to submucosal fat (asterisk); inflammation

is present between PVL and fat. (G) Invaginated surface, and front advancing at different levels and approaching salivary lobules (asterisk); the rectangled area is magnified in (H) to allow appreciation of cytology. (H) The proliferative keratinocytes are often differentiated, but mitoses (arrow), densely stained nuclei (arrowhead) and perturbed stratification with absence of basal layer can be seen (objective magnification ×10).

FIGURE 5

Kaplan Meier Cumulative malignant transformation rate_

TABLE 1

Hansen Histopathological grade of lesions for cohort, on initial and most recent biopsy

Table 2

Clinical characteristics and outcomes of PVL patients

Table 3. Transformed vs Non- transformed patients.

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Illustrative case of PVL. 79 year old female patient with longstanding history of PVL subject to two previous resections over 15 years for verrucous carcinoma (PVL grade 8). Presents with pan-oral lesions involving the mandulabar gingivae, with limited involvement of maxilla.

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(same case) A more significant lesion involves the floor of mouth and ventral tongue. Excision of this revealed verrucous carcinoma resected with narrow margins; the patient remains under close clinical review.

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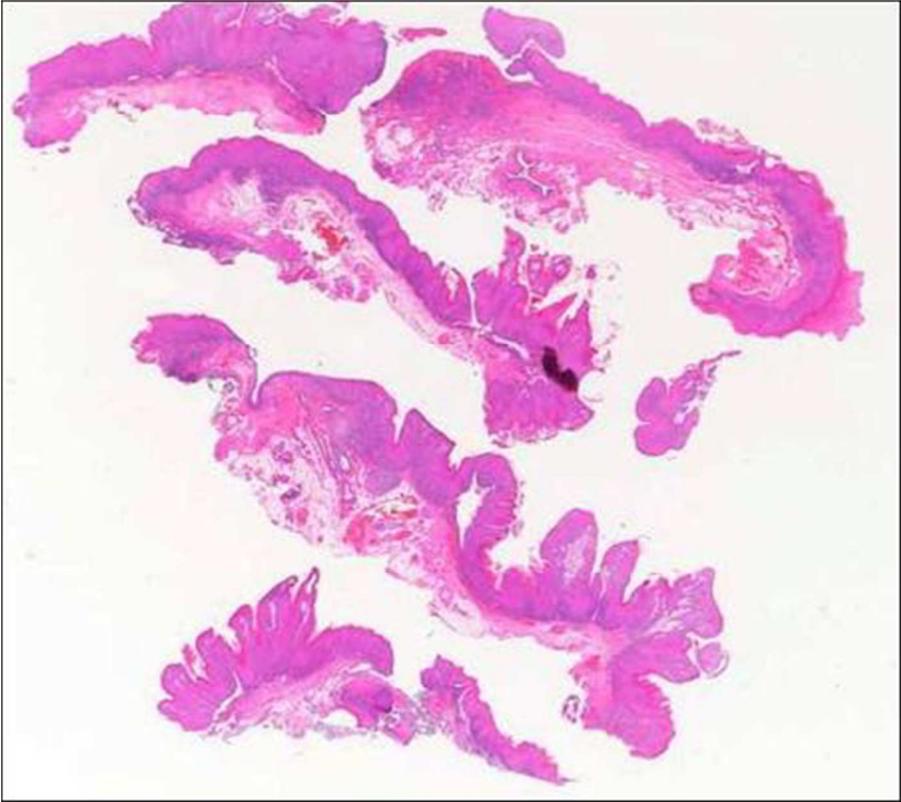
HNFig3- Caption : Scanned histological sections of the excised lesion shown in Figure 1, stained with hematoxylin and eosin. The limited extent of the excision can be appreciated.

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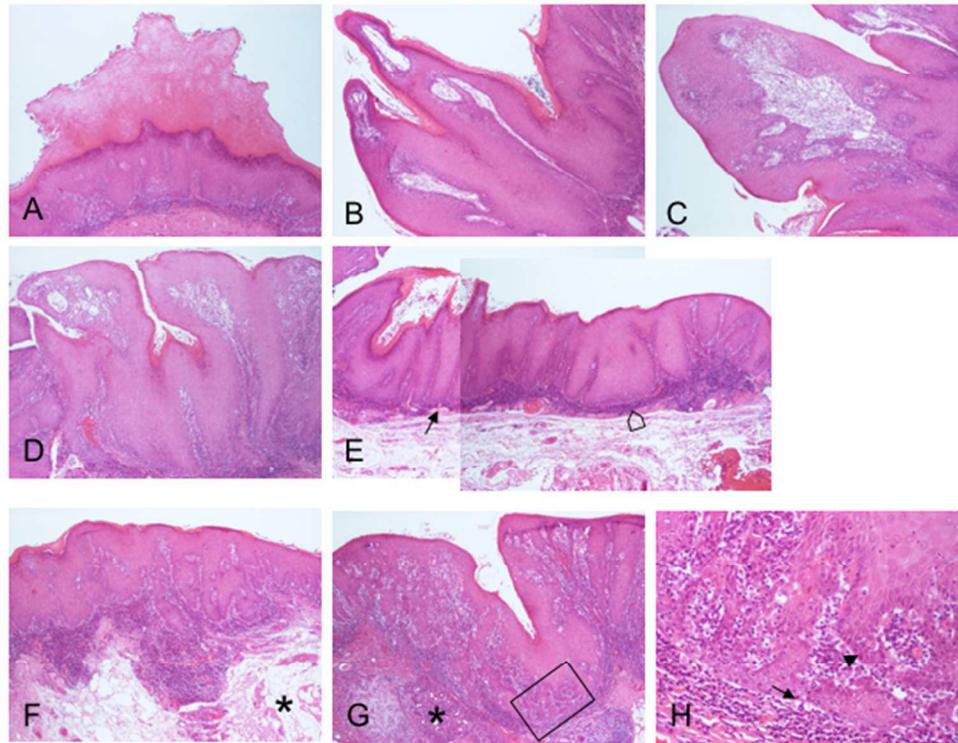
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: Areas of the sections shown in Figure 3 are magnified to illustrate the varying surface and front of PVL. (Unless otherwise specified, the photomicrographs were taken at a ×2 objective magnification.) (A) Compact, verrucous hyperorthokeratosis on the surface. (B) Finger-like exophytic papillary projections capped by hyperorthokeratosis, with 'shouldering' at the base. (C) Exophytic mammillated projection with inconspicuous keratinisation on the surface. (D) Focally infolded / invaginated surface. (E) Composite photomicrograph showing columns (arrow) and elephant feet-like arrangements (open arrow) of proliferative keratinocytes, which advance at more or less the same level; variable 'lichenoid' inflammatory reaction is sub-adjacent to the advancing front. (F) Gently mammillated surface, and front advancing at different levels, .though not extending to submucosal fat (asterisk); inflammation is present between PVL and fat. (G) Invaginated surface, and front advancing at different levels and approaching salivary lobules (asterisk); the rectangled area is magnified in (H) to allow appreciation of cytology. (H) The proliferative keratinocytes are often differentiated, but mitoses (arrow), densely stained nuclei (arrowhead) and perturbed stratification with absence of basal layer can be seen (objective magnification ×10).

Link text :

Image

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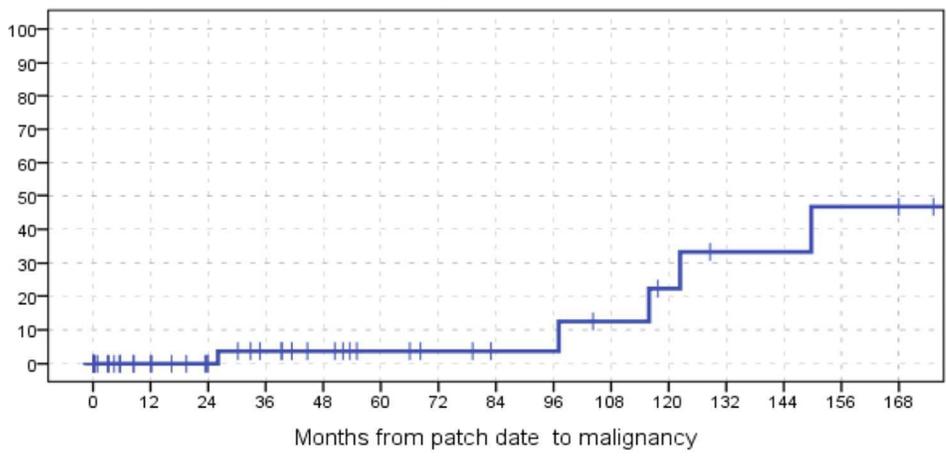
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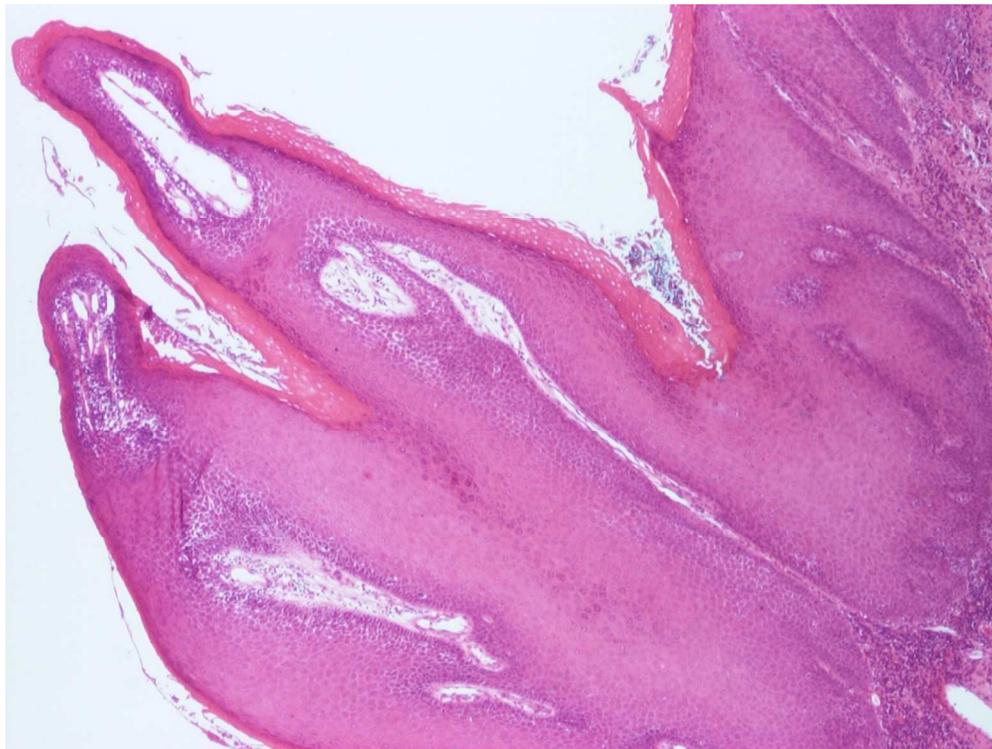
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Table 1
Hansen Histopathological grade of lesions for cohort, on initial and most recent biopsy

Biopsy Grade	Number of Patients	
	Initial	Most Recent*
1	-	-
2	2	-
3	14	5
4	14	12
5	9	9
6	5	9
7	-	1
8	1	3
9	3	9
10	-	-

*Footnote: 20 patients had one biopsy only

Table 2
Clinical characteristics and outcomes of PVL patients

	Silverman[1] N=54	Bagan[2] N=55	Liverpool N=48
Age	62 (22-89) (Mean/Range)	62+/-12 (Mean +/- SD)	70+/-13 (Mean +/- SD)
Followup (Years)	11.6 (1-39) (Mean/Range)	7.5+/-4.2 (Mean +/- SD)	4.3+/-3.7 (Mean +/- SD)
Male:Female ratio	1:4	1:2	1:1
Tobacco Users	31%	36%	69% (33/48)
Alcohol Users	Not reported	Not Reported	56% (27/48)
Surgical removal	79%(42/53)	100% (55/55)	8% (4/48)
Malignant transformation	70% (38/54)	49% (27/55)	48% (23/48)
Died of disease	40% (21/53)	Not reported	13% (6/48)

Table 3. Transformed vs Non- transformed patients.

		Transformed Group (T) N=23	Not Transformed Group (NT) N=25	Mann-Whitney Test
Age at time of PVL diagnosis (Years), median (IQR)		65 (57-73)	68 (56-75)	P=0.46
Gender male		52% (12)	48% (12)	P=0.99*
Smoking Status (Pack years), median (IQR)		15 (0-31)	6 (0-38)	P=0.99
Alcohol Consumption (Units/Week)		4 (0-8)	1 (0-16)	P=0.97
Subsite	Multifocal**	61% (14)	24% (6)	P=0.02**
	Gingiva	17% (4)	48% (12)	P=0.005***
	Tongue	13% (3)	12% (3)	
	Buccal	9% (2)	8% (2)	
	Other	0%	8% (2)	
Number of biopsies	median (IQR)	5 (4-10)	1 (1-3)	P<0.001
	1	0%(0)	56% (14)	
	2-5	47% (11)	44% (11)	
	6-10	34% (8)	0% (0)	
	11-30	15% (3)	0% (0)	
Size of lesion. Median (IQR)		750mm^2 (425-1500)	225mm^2 (100-575)	P=0.001

*Fishers Exact Test
**Fishers Exact Test: multifocal Vs rest
***Fishers Exact Test: gingiva Vs rest
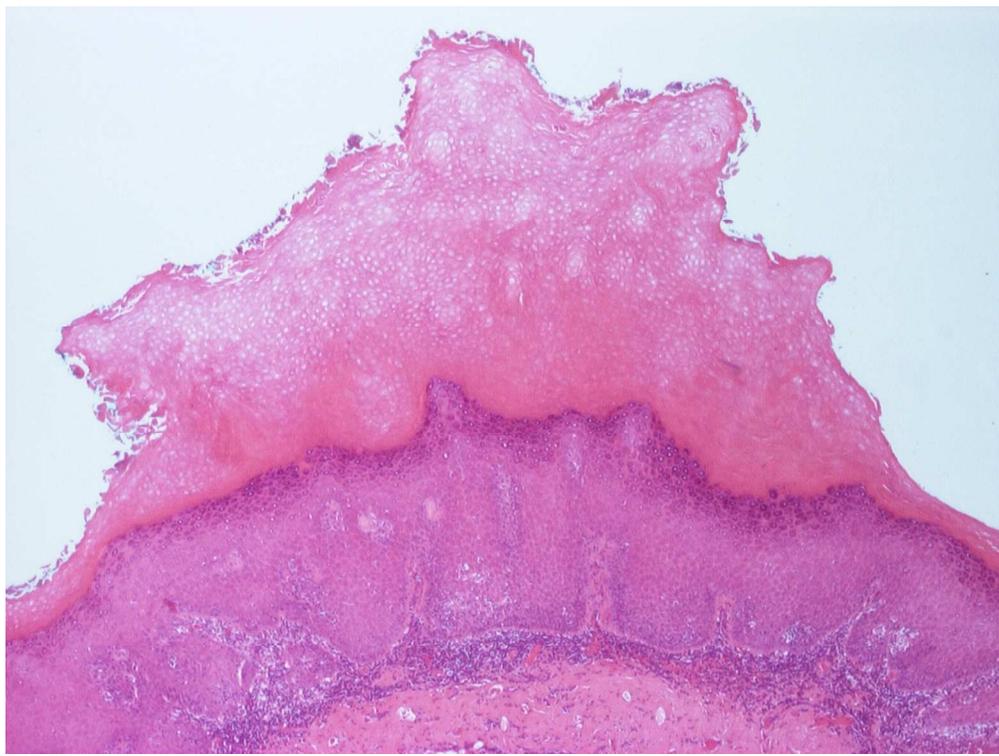
HNFig 4A -see composite

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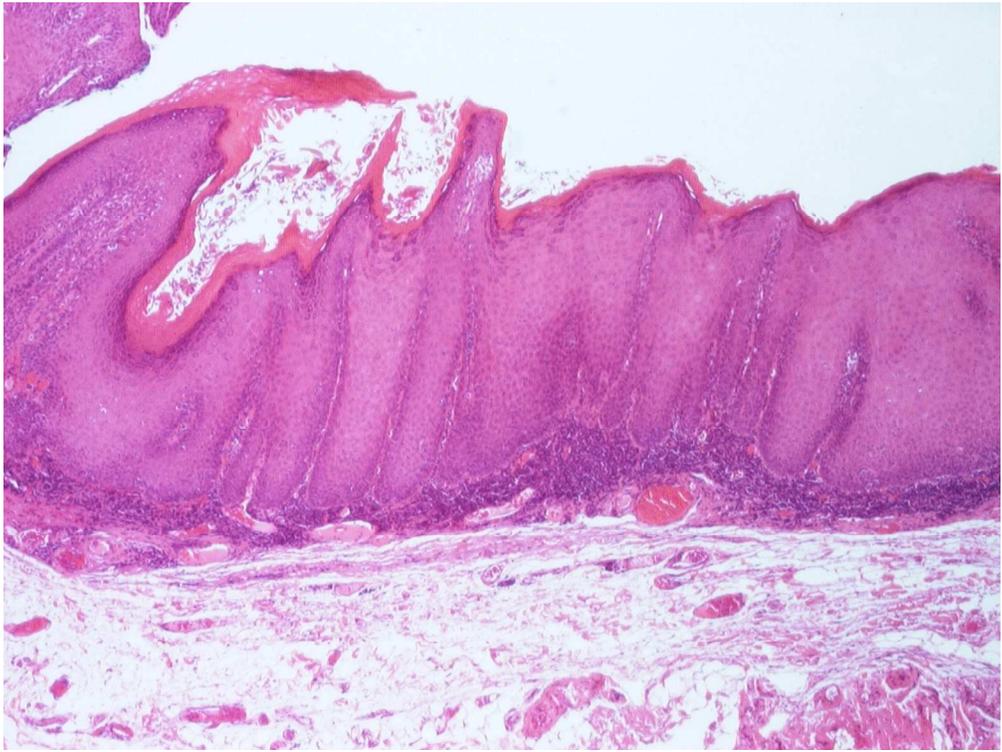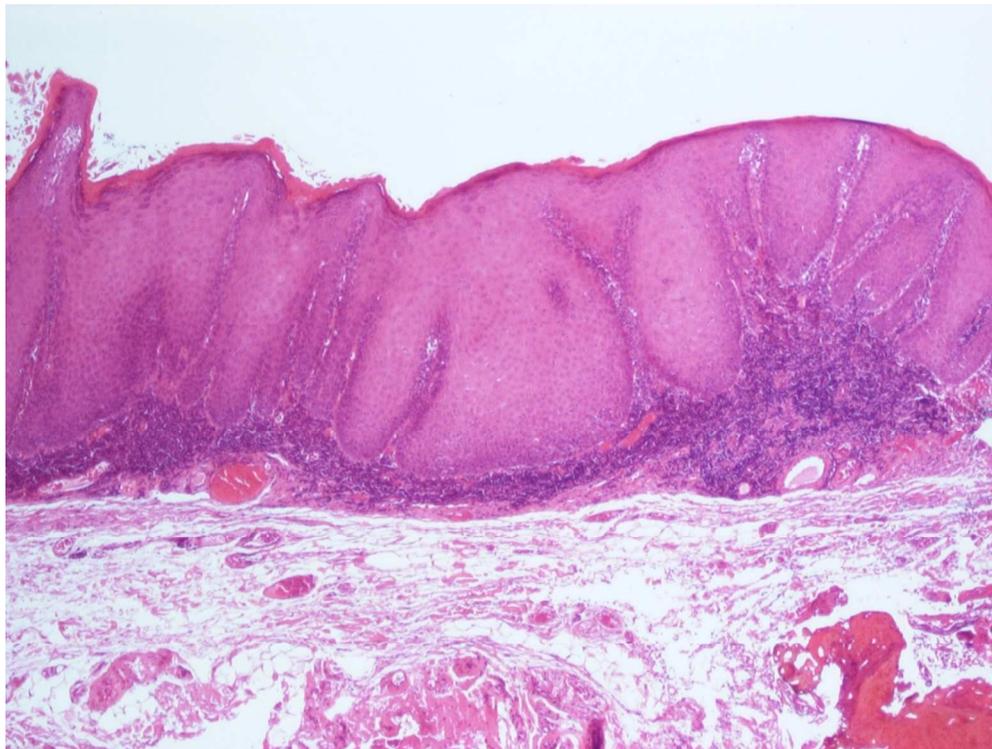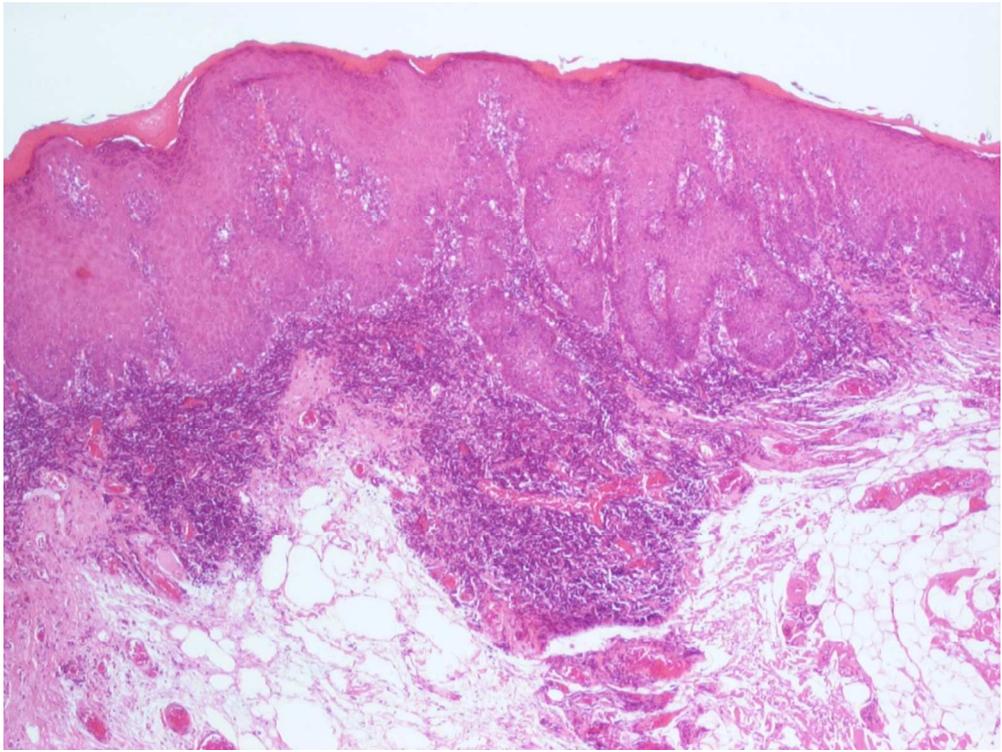
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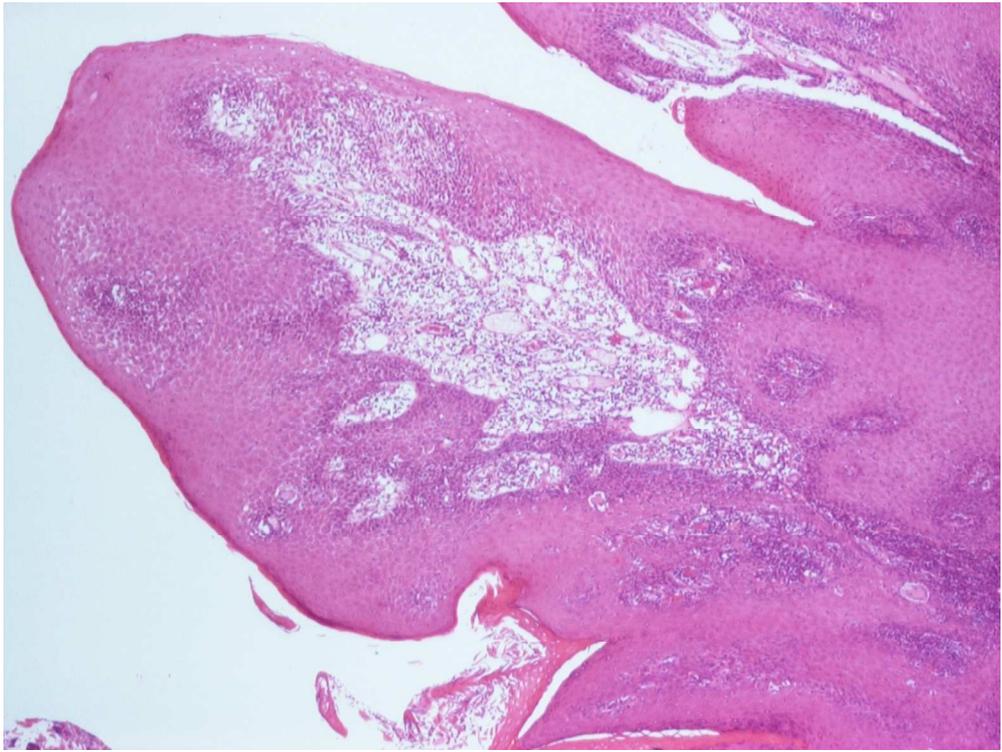
HNFIG4C -see composite

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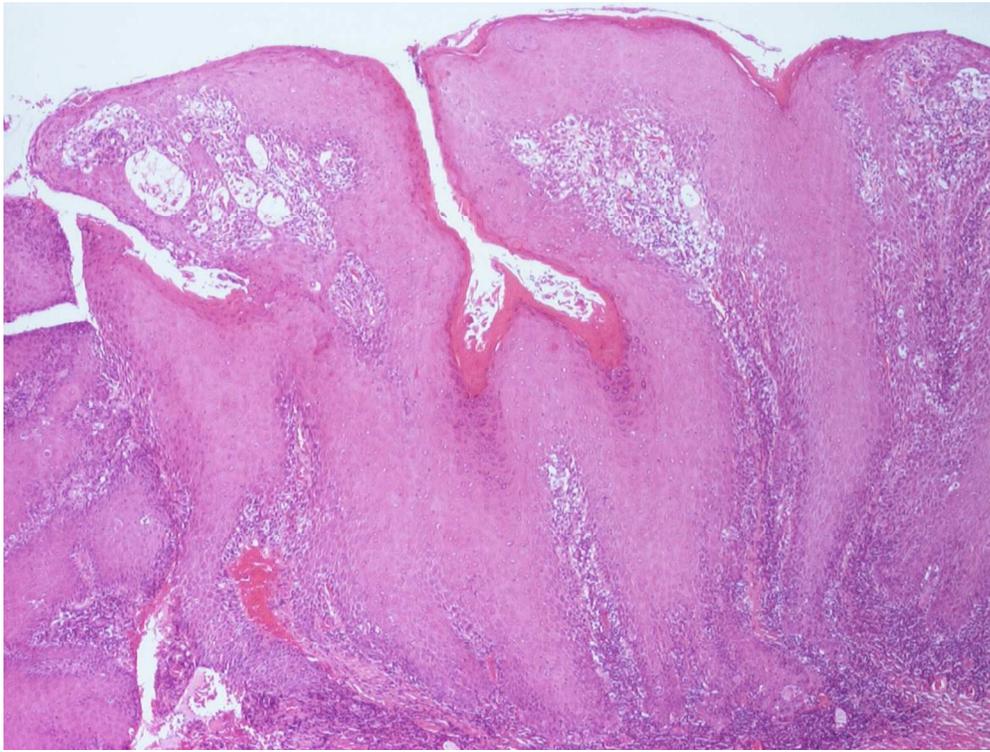
HNFIG 4D -see composite

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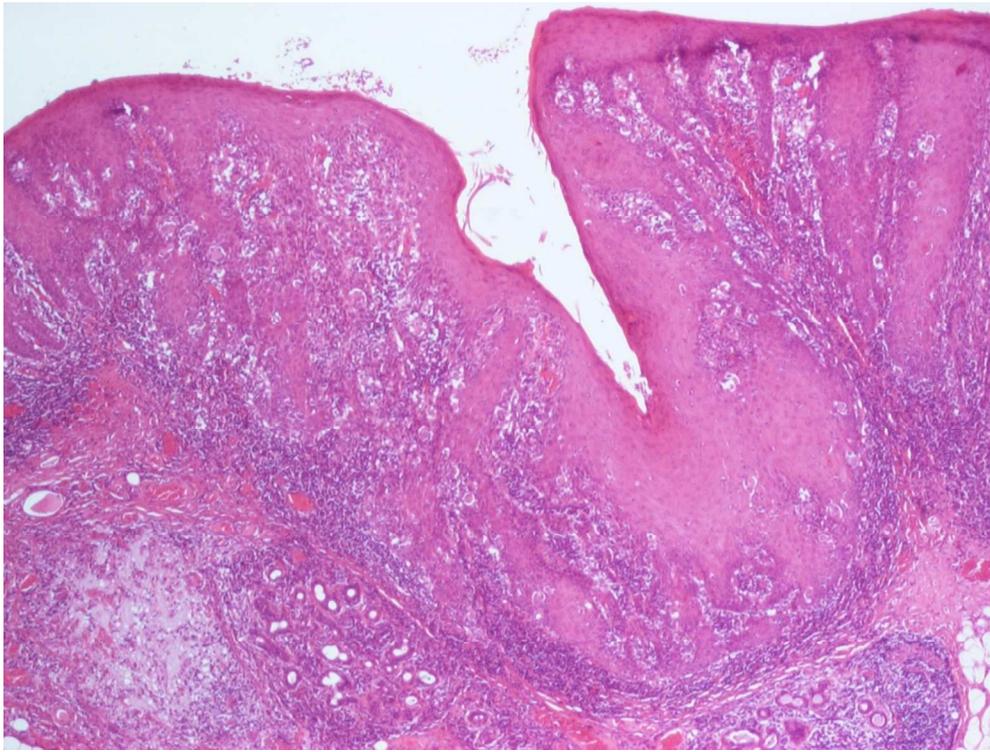
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HNFIG4Fsee composite

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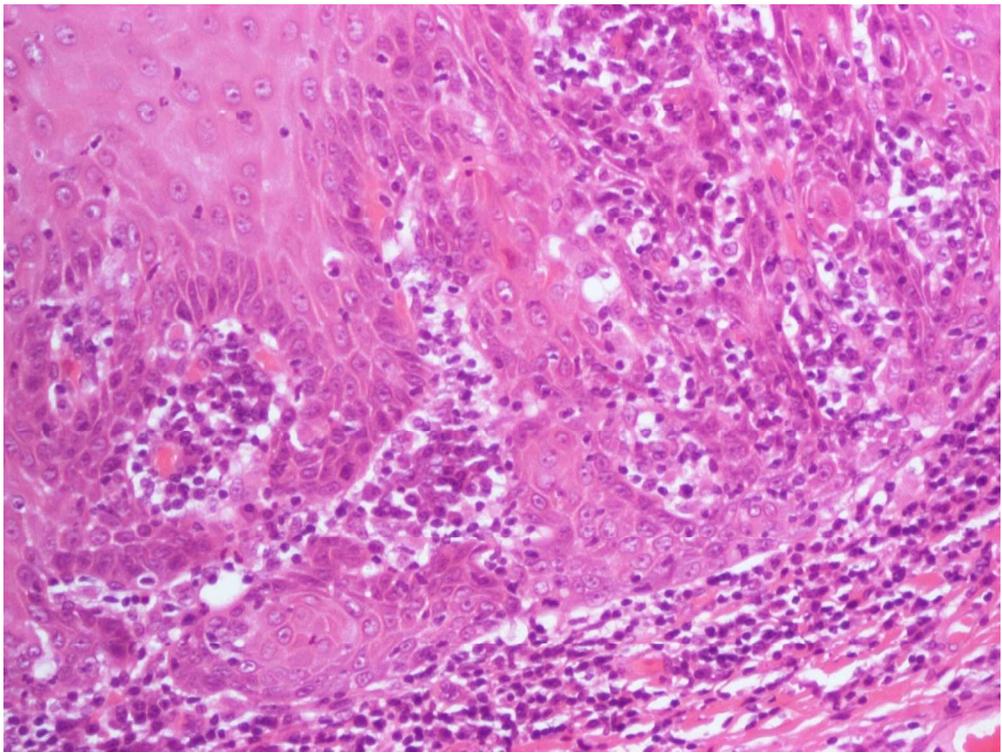47
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HN FIG 4Gsee composite

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HNFIG 4Hsee composite

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