Samuel Charles Miller Lecture
Leukoplakia and Proliferative Leukoplakia: Moving Forward

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Current definition of leukoplakia

• WHO definition (2007)
  • White plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer.

• Clinical term only, modified after histopathologic evaluation

• What it means:
  • Most (if not all) leukoplakias are precancerous
  • It excludes lesions where a specific etiology is known
Specific etiologies for white lesions

- Developmental (e.g. Cannon white sponge nevus)
- Infectious
  - Candidiasis and hairy leukoplakia
- Reactive
  - Retention keratosis (e.g. hairy tongue)
  - Contact/chemical irritation (e.g. dentifrices, foods)
  - Frictional/traumatic (e.g. nibbling, chronic contact)
- Immune-mediated/autoimmune
  - Lichenoid lesions (e.g. lichen planus, lupus erythematosus)
- Preneoplastic/neoplastic
  - Leukoplakia and SCCA
- Others
  - Biologic-agent induced (e.g. palifermin)
Pseudomembranous candidiasis

Median rhomboid glossitis
Hairy Leukoplakia
• No pre-malignant connotation
• Epstein Barr virus infection
• Immunocompromised pts such as in HIV/AIDS, post-organ transplantation
• ? Immunosenescence
• Chambers et al (QO 2015: 119:326)
  - 35 pts (mean age 61) - -
  - 28 long-term steroid inhalers
  - 4 autoimmune disease on immunosuppression,
  - 4 with DM
Hairy Tongue: Retention keratosis

• Dehydration
  - Poor PO intake (illness on abx)
  - Too much caffeine
  - Smoking
  - Alcoholic mouthrinses

• Soft diet
  - Illness
  - Personal reasons
Contact irritation

• Leukoedema
  • Contact with mild irritants (e.g. tobacco smoke, toothpaste)

• Contact desquamation
  • Tooth paste or other strong dentifrices (e.g. Listerine™, Prohealth™)
  • Chewing gum and candies, esp cinnamic aldehyde flavored (e.g. Fireballs)
  • Smokeless tobacco

• These are NOT leukoplakias.
Leukoedema
Contact desquamation
(from Listerine, ProHealth)
Two weeks after biopsy on R Smokeless Tobacco Lesions (? Keratosis) contact stomatitis

Two weeks after biopsy on R
Leukoplakia developing within Smokeless Tobacco Lesion
• Demarcated, fissured keratosis
  - leukoplakia

Courtesy of Dr. Jerry Bouquot, Texas, USA
Nicotinic stomatitis
• Cased by heat usually from pipe smoking

Courtesy of Dr. Linda Lee, Princess Margaret Hospital, Toronto

Courtesy of Dr. Ivan Stojanov, Case Western University
Morsicatio mucosa oris

- Chronic frictional/factitial keratosis
- On nonkeratinized mucosa
- Linea alba is mildest form
- Has specific histopathology, not just hyperkeratosis
Chronic frictional/factitial keratosis: all poorly demarcated with fading margins
Benign alveolar ridge (frictional) keratosis [BARK]

• Occurs on a **keratinized** site and most common is retromolar pad (usually bilateral), and edentulous ridge
• Oral counterpart of lichen simplex chronicus (LSC) of skin
• Has specific histopathology

Prevalence of Dyspl/Ca if frictional lesions excluded (by WHO definition): 72/168 = 43%
Prevalence of Dyspl/Ca if frictional lesions included: 72/703 = 10%
Keratosis of Unknown Significance: 57% of true leukoplakia
The Pathology Report

• Ideally, it should read:
  • Chronic frictional/factitial keratosis OR Reactive keratosis
  • Benign alveolar ridge (frictional) keratosis OR Reactive keratosis
  • This is a useful diagnosis for clinician because it provides etiology

• Often, it reads
  • Hyperkeratosis, acanthosis, no evidence of dysplasia
  • This is default diagnosis of leukoplakia
  • Should always discuss with your pathologist
Specific etiologies for white lesions

- Developmental (e.g. Cannon white sponge nevus)
- Infectious
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- Preneoplastic/neoplastic
  - Leukoplakia and SCCA
- Others
  - Biologic-agent induced (e.g. palifermin)
Lichen planus/Lichenoid mucositis

- I make a histopathologic diagnosis of LP when
  - All the histopathologic features are present (uncommon) OR
  - Major histopathologic features are present and clinically lesions are
    - Bilateral
    - Symmetric
    - White and reticulated (except for gingiva)
    - At the usual sites (buccal mucosa, tongue, gingiva)
- Otherwise, DX: Lichenoid mucositis c/w lichen planus in the appropriate context
- Classic LP with all features are only seen in peak of presentation, rare
- MUST correlate with clinical findings
- Histologic LICHENOID MUCOSITIS ≠ LICHEN PLANUS
- Often see as TLR (tumor lymphocytic response)
Red lesion – often desquamative gingivitis
Medications associated with lichenoid reactions

### Dermatology Literature
- Antihypertensive agents esp. diuretics (eg hydrochlortohiazide), beta blockers, ACE inhibitors
- Sulfonylureas
- Sulfasalazine
- Allopurinol
- NSAIDs
- Carbamazepine
- Gold salts
- Penicillamine
- Ketoconazole
- Lithium

### Oral Medicine Literature
- Antihypertensive agents esp. diuretics (eg hydrochlortohiazide), beta blockers, ACE inhibitors
- Sulfonylureas
- Levothyroxine
- Sulfasalazine
- Allopurinol
- NSAIDs
- Carbamazepine
- Some statins
- Newer drugs eg. biologics such as TNF alpha inhibitor

Grinspan syndrome: lichen planus, hypertension, diabetes mellitus
Is LP a specific disease?

Maybe LP/lichenoid process is a final common pathway in some inflammatory conditions
Lichen planus and malignant transformation

• Occurs in 0.1-1% depending on report
• Must exclude all smokers
• Must see classic LP i.e. bilateral, symmetric, reticulated, at the usual sites
Courtesy of Dr. Armando Gama, Montana
Leukoplakia

- WHO definition
  - White plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer (includes frictional keratosis)
- Most common manifestation of dysplasia
- Localized vs proliferative leukoplakia

Warnakulasuriya et al. 2007; 36:575-580
WHO Classification of Oral Potentially Malignant Lesions/Conditions

- Leukoplakia
  - Homogenous
    - Evenly white, may be fissured
  - Nonhomogenous
    - Red areas (erythroleukoplakia)
    - Nodular areas
    - Verrucous areas ( verrucous leukoplakia)
    - Proliferative verrucous leukoplakia?

# Localized Leukoplakia vs. Proliferative Leukoplakia

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Localized leukoplakia</th>
<th>Proliferative leukoplakia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Older men</td>
<td>Older women</td>
</tr>
<tr>
<td>Smoking association</td>
<td>Strong</td>
<td>Weak &lt; 30%</td>
</tr>
<tr>
<td>Number of sites</td>
<td>Single site</td>
<td>Extensive at one site (&gt; 3 cm); multi-focal sites</td>
</tr>
<tr>
<td>Location</td>
<td>Ventral tongue, floor of mouth</td>
<td>Gingiva, buccal mucosa</td>
</tr>
<tr>
<td>Prevalence of dysplasia</td>
<td>~ 40% at first biopsy</td>
<td>&lt; 10% at first biopsy (KUS)</td>
</tr>
<tr>
<td>Deletion in $p14^{ARF}$ exon 1β (within CDKN2A locus)</td>
<td>3.8%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Malignant transformation</td>
<td>3-15% develops SCCa</td>
<td>At least 70% develops SCCa</td>
</tr>
<tr>
<td>Treatment</td>
<td>Small, so excision or ablation fairly easy</td>
<td>F/U and surveillance biopsies; “recurrence” because of involved margins</td>
</tr>
</tbody>
</table>

KUS: Keratosis of Uncertain Significance
Risk factors for leukoplakia

Same as for SCCa

- Smoking
- Alcohol
- Areca nut chewing
- Immunosuppression (e.g. post-organ transplantation, HIV/AIDS)
- Personal h/o cancer
- Family h/o cancer (60-70%)
- Age
- Human papillomavirus (HPV)
- Sunlight (lip only)
- Syndromes (e.g. dyskeratosis congenita)
What is common to all these lesions clinically? Sharp demarcation at least partially; fissures.
Nonhomogenous leukoplakia
Proliferative verrucous and erythro-leukoplakia
How to evaluate oral epithelial dysplasia

- Architectural changes (lower power)
  - Verrucous architecture (all verrucous hyperplasias are dysplasias)
  - Bulky/Endophytic squamous proliferation
  - Hyperkeratosis and epithelial atrophy
  - Demarcated keratosis or “skip” areas
  - Bulbous rete ridges
- Organizational changes (medium-to high power)
  - Dyscohesion
  - Basal cell hyperplasia
  - Keratin pearls at tips of rete ridges
  - Mid-level mitotic figures
- Cytologic changes (high power cytology)
  - The usual

Atypical verrucous hyperplasia
This is dysplastic from architectural changes even if the word “dysplasia” does not occur in the path report
Hyperkeratosis, atypical verrucous epithelial hyperplasia; no dysplasia; proliferative leukoplakia.
Signed out as: parakeratosis, acanthosis and lichenoid mucositis, no dysplasia
My diagnosis: Atypical bulky squamous proliferation and Cl, not likely reactive
Biopsy from tongue dorsum

• Hyperkeratosis, papillary atrophy, chronic inflammation, not likely reactive or KUS
• This is not a lichen planus in spite of the band – basal cells intact
• Tumor-associated lymphocytic infiltrate
15 years later: SCCa rising from a KUS

Could cancer have been prevented if excised?
Oral keratoses

- Majority are frictional/factitial
  - Chronic frictional/factitial keratosis (morsicatio mucosae oris)
  - Benign alveolar ridge (frictional) keratosis
  - These are NOT leukoplakia
- If you receive a report of
  - Hyperkeratosis, acanthosis, chronic inflammation (KUS)
    - Check with the pathologist – is this reactive/frictional? Unsure?
    - Re-evaluate the patient
  - Hyperkeratosis and epithelial atrophy
    - Re-evaluate the patient
Could these be frictional?
Histologically, they were KUS
<table>
<thead>
<tr>
<th>All “Leukoplakia”</th>
<th>703</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive keratosis</td>
<td>535</td>
<td>76%</td>
</tr>
<tr>
<td>Morsicatio</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>BARK (oral LSC)</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Other, non-sp</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>True leukoplakia</td>
<td>168</td>
<td>24%</td>
</tr>
<tr>
<td>Dyspl/Ca</td>
<td>10% (72 cases)</td>
<td></td>
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<tr>
<td>KUS</td>
<td>14% (96 cases)</td>
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Prevalence of Dyspl/Ca if frictional lesions excluded (by WHO definition): 72/168 = 43%
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Keratosis of Unknown Significance: 57% of true leukoplakia
Recap

- Leukoplakias are a clinical diagnosis after excluding other conditions
- ~40% are dysplasia or cancer at the time of diagnosis
- Other ~60% are keratosis of uncertain significance (KUS) what a pathologist may call “Hyperkeratosis, no dysplasia”
  - ALWAYS correlate this diagnosis with clinical findings:
    - Sharp demarcation, fissuring (clonal lesions)
    - Poor demarcation with fading margins (likely reactive)
  - 16% of these become dysplasia and carcinoma over time
Keratosis of Uncertain Significance

- Unpublished data
  - They harbor similar mutations as dysplasia and SCCA
    - 15 cases of KUS (just hyperkeratosis)
    - 15 cases of proliferative leukoplakia
    - 15 cases of moderate/severe dysplasia
Keratosis of Uncertain Significance

Mutations

- CDKN2A 100%
- KMT2C 100%
- TP53 96%
- CCND3 100%
- NOTCH2 96%
- CYLD 96%
- PIK3CA 85%
- CCND1 85%

Normal cell

Genotypic dysplasia

Critical accumulation of genetic mutations

Phenotypic Dysplasia: Cytologic Architectural

Abnormal-appearing cells on microscopy

Invasive cancer

Normal-appearing cells on microscopy but hyperkeratotic (KUS)

KUS associated with invasive SCCA in 3-16% of cases
Three Strikes to Cancer

Breakthrough phase
A single cell develops a specific driver-gene mutation and begins to divide abnormally.

Expansion phase
A cell develops an additional driver-gene mutation that gives rise to a benign tumor.

Invasive phase
A cell develops an additional driver-gene mutation in at least one of the indicated pathways, enabling it to invade surrounding tissues.

Metastasis
Cancer is a genetic disease

- All cancers are genetic diseases
- Oral cancer is a genetic disease caused mostly by mutations in tumor suppressor genes and not oncogenes (e.g., $p53$, $CDKN2A$, $PIK3CA$)
WHO Classification of Oral Potentially Malignant Lesions/Conditions

• Leukoplakia
  • Homogenous
    • Evenly white, may be fissured
  • Nonhomogenous
    • Red areas (erythroleukoplakia)
    • Nodular areas
    • Verrucous areas ( verrucous leukoplakia)
    • Proliferative verrucous leukoplakia?

Proliferative verrucous leukoplakia

- Localized Leukoplakia
  - Homogenous
  - Non-homogenous
    - Erythroleukoplakia
    - Verrucous-nodular leukoplakia

- Proliferative Leukoplakia
  - Homogenous, fissured
  - Non-homogenous
    - Erythroleukoplakia (often mistaken for lichen planus, especially if the pathology showed lichenoid infiltrate)
    - Verrucous-nodular leukoplakia (PVL
Definition by Hansen et al.
Triple O1985;60:285-98.

- Slow-growing, persistent, irreversible lesion with erythematous components and exophytic and wart-like areas resistant to any treatment.
- Often starts as leukoplakia simplex (Grade 2) (KUS)

Is this still valid based on what we know now? Atrophy, dysplasia
Major (3 or 2 x 2 minor)

- A. > Two different oral sites, usually seen on the gingiva, palate and alveolar ridge
- B. Verrucous appearance
- C. Progression and spread
- D. Recurrence
- E. Oral epithelial hyperkeratosis or verrucous hyperplasia, verrucous carcinoma or squamous cell carcinoma at histological examination

Minor

- An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas
- Female
- Never smoker regardless of gender
- Disease evolution > 5 years

Diagnosis of PVL: 3 major (including E) or 2 major (including E) and 2 minor
<table>
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<th>Major (3 or 2 + 2 minor)</th>
<th>Minor</th>
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<td>• A. &gt; Two different oral sites, usually seen on the gingiva, palate and alveolar ridge.</td>
<td>• An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas</td>
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<tr>
<td>• B. Verrucous appearance (not always)</td>
<td>• Female</td>
</tr>
<tr>
<td>• C. Progression and spread</td>
<td>• Never smoker regardless of gender</td>
</tr>
<tr>
<td>• D. Recurrence (or progression of residual disease?) – impossible to eradicate because of location and size</td>
<td>• Disease evolution &gt; 5 years</td>
</tr>
<tr>
<td>• E. Oral epithelial hyperkeratosis or verrucous hyperplasia, verrucous carcinoma or squamous cell carcinoma at histological examination (hyperkeratosis and verrucous hyperplasia seen in reactive conditions)</td>
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</table>
2 weeks after biopsy

One year later; Courtesy of Dr. John Sexton
Proposed criteria

• Multi-site involvement or a single/contiguous site > 3 cm (arbitrary); exact site not so important
• Often verrucous/nodular, but may be homogenous/fissured or erythematous
• Biopsy initially may show hyperkeratosis or parakeratosis that is NOT reactive/frictional and does not fit any other known histologic entity (e.g. lichen planus), or dysplasia
• Enlarging or involving other sites over months and years
Pathology: hyperkeratosis and lichenoid mucositis. Is this lichen planus? Only site involved in mouth.
Does this qualify for PL? Minor: never smoker, female; Major: Not verrucous, not multi-site, did not recur because we did not treat it, + hyperkeratosis, pt said not progressing. By Cerera criteria, no.
Proliferative leukoplakia, all biopsies showed no dysplasia
Developed two cancers after 7 years of follow-up
Proliferative erythro-leukoplakia or lichen planus?
Is this lichen planus or proliferative erythro-leukoplakia
HPV Oral Dysplasia

- Presents as conventional leukoplakia
  - Almost always male, median age 60, most common location ventral tongue
  - Brightly eosinophilic parakeratin, severe dysplasia, prominent apoptosis and karyorrhexis (HPV-cytopathic effect well-seen in Heck disease)
  - Surrogate marker is P16; most are HPV-16*
  - Development of invasive SCCA in 15% of cases

Lerman et al. Mod Pathol 2013;26:1288-1297
HPV-associated severe dysplasia
Management of localized leukoplakia

• All dysplastic lesions should be excised, with clear margins, if clinically appropriate (e.g. dysplasia in older patients, medically unstable, size)
  • Misconception that dysplastic lesions will regress; reactive atypias regress
• If KUS, conservative or narrow excision should be considered, if well-demarcated plaque.
  • Wide excision of “recurrent” lesions
  • Does your pathologist report on margin status for dysplasia? Does she/he report on KUS at the margin?
• Best oral cancer prevention – remove KUS and small dysplastic lesions when you can
2-stage excision

KUS: Narrow excision

KUS: Wide re-excision
Conclusions

• Leukoplakia and proliferative leukoplakia are clínico-pathologic entities; both are genetic diseases

• Keratosis of uncertain significance (hyperkeratosis, not reactive) must always be correlated with clinical findings

• Proliferative leukoplakia is often but not invariably verrucous (maybe homogenous or erythro-leukoplakia), is a different entity from conventional localized leukoplakia
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