Laryngeal leukoplakia

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laryngeal leukoplakia

- Histopathology
- Etiology
- Predictor for progression
- Treatment
Introduction

- Leukoplakia: A chronic white mucosal macule which cannot be scraped off, cannot be given another specific diagnostic name
- White lesions: leukoplakia, hyperkeratosis, pachydermia and epithelial hyperplastic lesion
- Difficult to predict which white lesion progress into carcinoma
- Little correlation with underlying histopathology
Biopsy of leukoplakia?

Yes, to rule out carcinoma
Histopathologic classification

- 3 different levels of histopathological changes:
- Hyperplasia: thicker epithelium without any change in maturation
- Metaplasia: one epithelium transformed into another epithelium
- Dysplasia: changes in the epithelial differentiation with cell atypia and citomorphological disorder
normal epithelium
Hyperplasia
Metaplasia

Respiratory epithelium metaplasia to squamous epithelium

Normal respiratory epithelium
Dysplasia

Hyperchromasia, N/C ratio ↑, cell crowding with loss of cellular polarity
Kleinsasser classification:

Kleinsasser classification of dysplasia (1963):

Degree I: simple hyperplasia + absence of dysplasia or mitotic and cellular atypia
Degree II: hyperplasia + dysplasia and cellular atypia
Degree III: cancerization (carcinoma in situ)
Resta L. (1987):

1st group: hyperplasia of basal cells, simple keratosis, acantosis and hyperplasia of the thorny layer

2nd group: laryngeal intraepithelial neoplasia (LIN)

   LIN I: mild dysplasia
   LIN II: moderate dysplasia
   LIN III: severe dysplasia
   CIS: carcinoma in situ
Mild dysplasia

Moderate dysplasia

Severe dysplasia
Etiology

- Biological factors
- Environmental factor
Biological factors:

- Sex: hormonal factor of androgenic type
- Avitaminosis: deficit of Vit. A (controlling epithelial differentiation)
- Local irritating factor: chronic infections of sinuses, pharyngotonsil
- Vocal abuse: phonatory trauma
Environmental factor:

- Tobacco: constant and long term irritation
- Alcohol: direct and indirect effect of vascular system causing chronic congestion of larynx
- Toxic gas, mineral dusts
- Irradiation exposure
### Table 1. REPORTED RELATIVE RISKS FOR DEVELOPING LARYNGEAL CARCINOMA WITH TOBACCO USE

<table>
<thead>
<tr>
<th>Tobacco Type</th>
<th>Relative Risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td>(less than 50 pack-years)</td>
</tr>
<tr>
<td></td>
<td>9.1</td>
<td>(more than 50 pack-years)</td>
</tr>
<tr>
<td></td>
<td>6.0</td>
<td>(less than 30 cigarettes/day)</td>
</tr>
<tr>
<td></td>
<td>19.2</td>
<td>(more than 40 cigarettes/day)</td>
</tr>
<tr>
<td></td>
<td>9.6</td>
<td>(less than 45 pack-years)</td>
</tr>
<tr>
<td></td>
<td>11.3</td>
<td>(more than 45 pack-years)</td>
</tr>
<tr>
<td></td>
<td>14.7</td>
<td>(light tobacco)</td>
</tr>
<tr>
<td></td>
<td>35.4</td>
<td>(dark tobacco)</td>
</tr>
<tr>
<td></td>
<td><strong>11.8</strong></td>
<td>(less than 20 cigarettes/day)</td>
</tr>
<tr>
<td></td>
<td><strong>13.5</strong></td>
<td>(less than one pack per day)</td>
</tr>
<tr>
<td></td>
<td><strong>34.4</strong></td>
<td>(more than two packs per day)</td>
</tr>
<tr>
<td>Chewing tobacco</td>
<td>7.7</td>
<td>(Laryngeal and oral squamous cell carcinoma included)</td>
</tr>
<tr>
<td></td>
<td>40.0</td>
<td>(smoking and chewing tobacco)</td>
</tr>
<tr>
<td>Cigars/pipe</td>
<td>22.0</td>
<td>Rothman et al(^{82})</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>(cigars and/or pipe alone)</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>(cigars/pipe and cigarettes)</td>
</tr>
</tbody>
</table>

### Table 2. REPORTED RELATIVE RISKS FOR DEVELOPING LARYNGEAL CARCINOMA WITH ETHANOL CONSUMPTION*  

<table>
<thead>
<tr>
<th>Variables Studied</th>
<th>Relative Risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td>3.2</td>
<td>Herity et al(^{143})</td>
</tr>
<tr>
<td>Smokers</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>4.6</td>
<td>Stevens et al(^{96})</td>
</tr>
<tr>
<td>Smokers</td>
<td>26.0</td>
<td></td>
</tr>
<tr>
<td>Moderate drinkers</td>
<td>7.7</td>
<td>DeStefani et al(^{22})</td>
</tr>
<tr>
<td>Heavy drinkers</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>Moderate drinkers</td>
<td>2.6</td>
<td>Maier et al(^{82})</td>
</tr>
<tr>
<td>Heavy drinkers</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Moderate drinkers</td>
<td>0.8</td>
<td>Olsen et al(^{74})</td>
</tr>
<tr>
<td>Heavy drinkers</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Moderate drinkers</td>
<td>1.7</td>
<td>Wynder et al(^{117})</td>
</tr>
<tr>
<td>Heavy drinkers</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Moderate drinkers</td>
<td>2.0</td>
<td>Falk et al(^{27})</td>
</tr>
</tbody>
</table>

*All of these studies were controlled for tobacco use.
Predictor for progression


**FIGURE 1.** The methionine cycle and its metabolic links with nucleotide synthesis and DNA methylation pathways. THF: tetrahydrofolic acid; MTHFR: methylenetetrahydrofolate reductase; MS: methionine synthase; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine.
**Serum Levels of Folate, Homocysteine, and Vitamin B₁₂ in the Control Groups, in Patients with Head and Neck Squamous Cell Carcinoma, and in Patients with Laryngeal Leukoplakia**

<table>
<thead>
<tr>
<th>Group</th>
<th>Folate</th>
<th>Homocysteine</th>
<th>Vitamin B₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level (ng/mL)*</td>
<td>Q score</td>
<td>Level (μmol/L)*</td>
</tr>
<tr>
<td>HNSCC group</td>
<td>4.87 ± 2.26</td>
<td>23.644</td>
<td>13.4 ± 10.2</td>
</tr>
<tr>
<td>Nonsmoker controls</td>
<td>9.7 ± 2.2</td>
<td></td>
<td>8.7 ± 3.9</td>
</tr>
<tr>
<td>HNSCC group</td>
<td>4.87 ± 2.26</td>
<td>19.048</td>
<td>13.4 ± 10.2</td>
</tr>
<tr>
<td>Smoker controls</td>
<td>9.1 ± 2.7</td>
<td></td>
<td>9.1 ± 5.0</td>
</tr>
<tr>
<td>Leukoplakia group</td>
<td>5.46 ± 2.12</td>
<td>14.052</td>
<td>8.45 ± 2.29</td>
</tr>
<tr>
<td>Nonsmoker controls</td>
<td>9.7 ± 2.2</td>
<td></td>
<td>8.7 ± 3.9</td>
</tr>
<tr>
<td>Leukoplakia group</td>
<td>5.46 ± 2.12</td>
<td>11.59</td>
<td>8.45 ± 2.29</td>
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<tr>
<td>Smoker controls</td>
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<td></td>
<td>9.1 ± 5.0</td>
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<tr>
<td>HNSCC group</td>
<td>4.87 ± 2.26</td>
<td>0.891</td>
<td>13.4 ± 10.2</td>
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<td>Leukoplakia group</td>
<td>5.46 ± 2.12</td>
<td></td>
<td>8.45 ± 2.29</td>
</tr>
</tbody>
</table>

HNSCC: head and neck squamous cell carcinoma; NS: not significant.

*Values shown are the mean ± standard deviation levels.

**Folate ↓; homocysteine ↑ (in HNSCC)**

**Vit B₁₂: no difference**
should the lesion be treated medically?
Blackwell KE:
Dysplasia → carcinoma:
mild dysplasia: 2% to 12%
moderate dysplasia: 9% to 33%
severe dysplasia: 13% to 44%
→ Treatment depend on the risk ratio
Treatment

- Elimination of risk factor and conservative treatment
- Retinoids therapy
- Photodynamic therapy
- One month trial of conservative measures
Treatment

- Elimination of risk factor:
  - Tobacco and ethanol abuse
  - Diet and vitamin deficiency
  - Irradiation exposure
  - Viral exposure (HPV)
  - Laryngopharyngeal reflux

- Conservative treatment:
  - Proper hydration
  - Reduction of caffeine (dehydrant)
  - Elimination of vocal abuse
Treatment

- Retinoids therapy:
  - Issing: loading dose (300000IU/day) for weeks + maintenance dose (150000IU/day) → 75% (15/20) complete response
  - Side effect (mucocutaneous toxicity) + recur after discontinuing medication
  - Hong et al: 10% spontaneous remission
    - 67% lesion size ↓ after treatment
Treatment

- Sieron A.: Photodynamic therapy
- Photosensitizer: Delta-aminolaevulinic acid (ALA) systemically or topically
- Argon-pumped dye laser (dose range: 100-250 J/cm², wavelength: 635 nm)
- Complete response rate: 10/12 (2003 otolaryngol Pol.)
- Better choice of laryngeal cancer(?)
Treatment

One month trial of conservative measures:

- Increased size
- Long duration
- Surface granularity
- Erythroplasia or ulceration

→ excisional biopsy
Conclusion

Leukoplakia: difficult to predict which white lesion progress into carcinoma and little correlation with underlying histopathology

Should the lesion be biopsied?

→ for diagnosis and r/o cancer

Complete excision or random biopsy?

→ excisional biopsy due to multicentricity of cancer
Conclusion

Any medical options to treat leukoplakia or conservative measure?
→ Depend on the risk ratio


Reference

