

The Frosted Applique', Filigree, Plaque: Lingual Algorithm

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Abbreviations

SCC: Squamous Cell Carcinoma; TGF: Transforming Growth Factor; EGFR: Epidermal Growth Factor Receptor; HIV: Human Immunodeficiency Virus; EBV: Epstein Barr Virus; HPV: Human Papilloma Virus

An aforesaid of a possible malignancy, the approximate evolution of dysplastic leukoplakia is 5%, adventing transparent or gray patches or thick, raised plaques with one raised margin, white patches, speckled and raised red margins, white lumps and dark red patches with irregular or a non-consistent texture, impinging on the gingiva, inner lining of the cheeks, inferior surface of the tongue, floor of the mouth, and tongue, epithelial atypia being the diagnostic criterion on tissue biopsy.

Oral SCC is accessorized by premalignancies and malignancies in 15% to 48%. Oral leukoplakia, defined as a "white patch (WHO 1978) or a plaque which cannot be characterized clinically or pathologically as any other disease". unaided by any physical or chemical basis except smoking and is the likeliest premalignancy/malignancy. Leukoplakia, a clinical diagnosis is defined by elimination of white lesions, e.g. oral lichen planus, white sponge nevus, nicotine stomatitis, leukoedema. A contemporary annotation (2012) "A predominantly white lesion or a plaque of questionable behaviour, having excluded clinically and histopathologically, any other definable white disease or disorder" with a 1.7 to 2.7% prevalence. The predicament is more prevalent in men and escalates with age. Complicates mastication, deglutition or jaw movements, are non-healing ulcers of 2 weeks or more, tissue metamorphosis in the mouth, aural pain/popping with deglutition.

Aetiology

Oral leukoplakia is a multifactorial affliction with higher incidence in smokers than non-smokers, along with Alcohol consumption. Dental restoration, Mechanical irritation, disease demonstration and amelioration with Human Papilloma Virus infection. a first symptom with Human Immunodeficiency Virus infection, Chemotherapy, Mononucleosis or Epstein Barr Virus, Organ surgery, Weak immune system, Recurrent ulcers, Consumption of hot foods /liquids. Excessive use of abrasive oral products, Oral whiteners or polishing devices, Poorly fitting dentures, braces, bites, plates or retainers, Jagged or rough teeth surfaces, Extended use of steroid inhalers without a mouth rinse, Poor oral hygiene, Cheek or tongue biting, Chewing certain nuts and leaves i.e. areca/betel.

Clinical Synopsis

Identifiable are homogenous type emerging as a flat, white, lesion. The non-homogenous inclusive of the Nodular and Verrucous Leukoplakia. The speckled type is externally white, red and white lesion. Verrucous leukoplakia has an elevated, proliferative, corrugated surface. The nodular type has small, polypoid outgrowths, rounded, chiefly white excrescences. Proliferative verrucous leukoplakia is a rare subtype of verrucous leukoplakia, describing an aggressive evolution, resistance to treatment, a higher degree of recurrence with a high rate of malignant transformation. Proliferative verrucous hyperplasia commences in a brief period, as a homogenous leukoplakia and disperses to the gingival, buccal mucosa, alveolar ridges. Of uncertain aetiology associated with HPV and EBV which is also implicated in

lymphoproliferative disorders, nasopharyngeal carcinoma. B cell lymphoma, lymphoepithelial carcinoma The lesion tends to be multicentric. Oral leukoplakia is misconstrued with the likeness of Candida (yeast). Hairy leukoplakia displays fuzz.

Histopathology

Evaluation of oral leukoplakia by Excisional biopsy or Brush biopsy, diversifies between dysplasia and carcinoma. Dysplasia echoes histological changes due to loss of uniformity/architecture of the epithelial cells, analogous to disturbed cell proliferation or disordered maturation. A proposed, histological binary classification (2010) categorized as Low risk and Moderate or Severe risk, with non-dysplastic and dysplastic (mild dysplasia, moderate and severe).

Increased cell/nuclear volume and pleomorphism
Hyperchromatic nuclei with hyperplastic basal cells
Increased nucleocytoplasmic ratio with enlarged nucleoli
Premature keratinisation of independent cells
Mitosis over basal layer with increased mitotic index
Enlarged /fused epidermal ridges
Loss of cell polarity
Decreased cell adhesion

Table 1: Pathologic Features of Dysplastic Oral Epithelium.

Malignant Transformation: Malignant Transformation is of an annual average of 1% and geographic areas are at a higher index of 43%. Epithelial dysplasia is (as was 20 years back) the accepted norm for conclusive malignant transformation. 36% of the dysplasias and 16% of the non dysplasias proceed to cancer. Dysplasia coordinated with clinical heterogeneity is maximally hazardous.

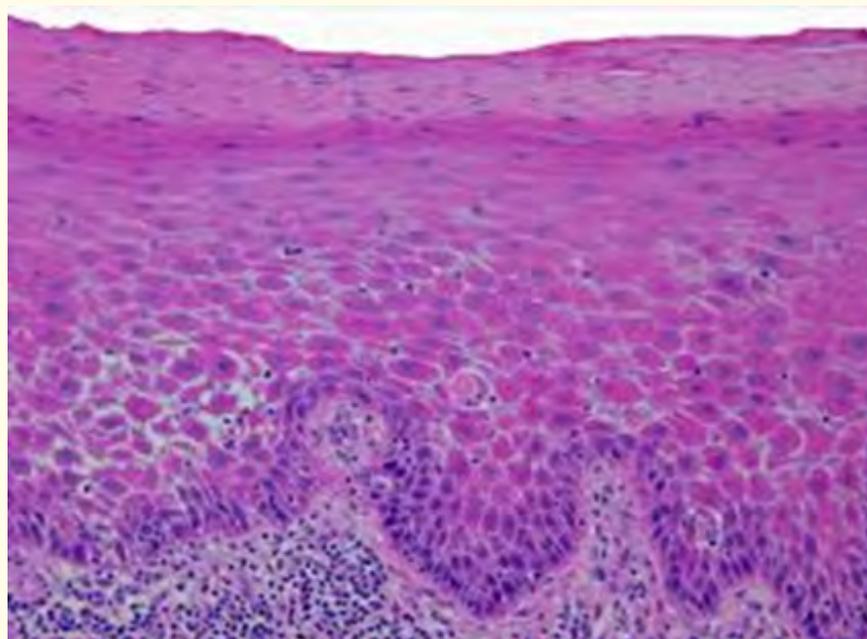


Figure 1: Dysplastic Leukoplakia.

Biomarkers: Biomarkers for appraisal of dysplasia/oral carcinogenesis is principled on proliferation marker Ki67 and component of cell cycle control such as tumour suppressor protein p53, the retinoblastoma protein pRb and cyclin D1. Expression of p53, and loss of expression of p16 are delineated the antecedents in malignant transformation. In non-dysplasia, a combined alteration of p53/Ki67/p16INK4a establish chances of tumour development. Furtherance to neoplastic prediction is the mucosal cell perimeter and the nuclear perimeter size. The artistry is of a morphometric analysis of computer generated, histological images. Consequent to the oral leukoplakia without cell atypia predicting oncogenic potential are:

- 1) Loss of Heterozygosity or Microsatellite Instability: Maturate in chromosomal regions with tumour suppressor genes. 3p and 9p with intermediate risk. And 4q,8p, 11q,3q,17p at high risk.
- 2) Aneuploidy: Unstable cells analyzed by flow cytometry. 70% diploid lesions are at low risk, 13% tetraploid lesions are intermediate risk, high risk are 17% of all dysplasia.
- 3) p53: Mutations in p53, a tumor suppressor gene is the conventional genetic abnormality in neoplasia. Cell death induction is by apoptosis (with a high cellular content) of p53. Cumulative positivity seen by immunohistochemistry and molecular assays necessitated to establish prognostic value. 53% of the patients have p53 mutation.
- 4) Telomerase activity in Leukoplakia: Human Telomerase reverse transcriptase (hTERT), gene overexpresses in leukoplakia and there is an accrued telomerase activity in the precancerous stage.
- 5) Microarray analysis allows the whole genome to be gauged and compares healthy tissue with the dysplastic. Overregulated genes in the dysplasia are cyclooxygenase 2 (COX-2), decorin transcript variant 2, arachidonate5-lipooxygenase, arachidonate12-lipooxygenase, prostaglandin E synthase.
- 6) Tissue Markers: i) Cell surface carbohydrates i.e. Blood Group Antigens, ABO, Lewis and T/Tn Loss of expression of A and B escalate tumour cell motility, matrigel invasion. ii) Keratins cytoskeletal proteins number 1 to 20. Loss of differential keratin expression in dysplastic lesions co-relate with a preminent risk of SCC transformation iii) Integrins: cell-cell and cell-extracellular matrix signalling process. Receptors comprises of 22 subunits of alpha & beta. Expression abates in SCC in contrast to dysplastic leukoplakias-signalling a poor prognostication. iv) Granulocyte colony stimulating factor receptor: Expanded expressivity in dysplasia and SCC. v) Growth factor receptor: Overexpression of TGF alpha seems parallel with the intensity of oral dysplasia. EGFR staining augments in extensive dysplasia. vi) Cell cycle regulators: Loss of p16 on gene 9p21 is the first gene to be deactivated in SCC. Also, cyclin D1 was amplified in 70% of the leukoplakias that evolved to SCC.

Matrix Metalloproteinases: 20 proteolytic enzymes essential for tissue remodelling, metalloproteinases 1 and 9 headed to SCC.

Extracellular Matrix Metalloproteinases Inducer: Expression of CD147 and M6 is categorically connected with degree of dysplasia.

Vascular Endothelial Growth Factor (VEGF): Metalloproteinase 11 and VEGF is in concordance with breakthrough of dysplastic leukoplakia to SCC.

Non-Invasive Methods of Investigation: Clinical review of the oral mucosa. Brush biopsy which amasses the basal layer. availing a brush- appropriate for mass screening. Toluidine blue as an intravital stain for nucleic acid, and abnormal tissue, applicable as a guidance for biopsy site ratification. Chemiluminescence (reflective tissue fluoroscopy) ascertains a conglomeration of oral mucosal lesions such as linea alba, hairy tongue, leukoedema, traumatic ulcers etc. Oral leukoplakia has an immense discernibility and sharpness with conspicuous and distinguished mucosal margins. Regrettably, these schematics do not bestow an explicit diagnosis. They are fundamentally applicable in the estimation of multicentricity and the non-compliant patient.

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Prevention: Tobacco/alcohol cessation, desisting inhaled or smoked products e.g. cannabis, clove, resin, routine self or clinical exam, routine dental exams and cleaning, abstaining from abrasive dental hygiene products such as whiteners and rinses, confirming cavities are filled properly and are not uneven/rough, assuring dental devices such as dentures and braces, fit well without uneven and stripped edges, preserving mouth wounds, cooling hot food/drinks, evading candies and irritating chewing products with jagged edges, consuming healthy, balanced diet to avoid nutritional imbalance/deficiencies, circumventing allergens.

Treatment: Cessation of smoking/alcohol intake. Histopathological evaluation: Low malignant potential (no/simple dysplasia) relies on the location, size, smoking cessation. The lesion may/may not be excised in to. Moderate/Severe dysplasia: Surgical treatment such as conventional surgery, laser ablation, electrocauterization, cryosurgery is advocated. Recurrence after surgery is 10% The medical treatment is local/systemic chemotherapy Chemoprevention with instruments such as vitamin A/retinoids. systemic beta carotene, lycopene, ketorolac (mouthwash), bleomycin and a mixture of tea topically and systemically is justified. Clinical and histological surveillance with frequent visits and biopsies are anticipated. Antivirals are designated to cases incident to HIV/EBV infection. The management of proliferative verrucous hyperplasia ranges from observation, topical chemoprevention to integral surgery. No satisfactory treatment has been evinced for leukoplakia so far [1-8].

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