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Journey of Leukoplakia So Far – An Insight on Shortcomings of Definitions and Classifications

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Abstract

Leukoplakia is one of the most frequently encountered white lesions by the clinicians. The definitions and terminologies associated with leukoplakia have been proposed by various authors. Also, various attempts have been made to clinically and histopathologically grade leukoplakia by evaluating different criteria.

Although there are numerous reviews that have discussed the definitions and classifications of leukoplakia, none has attempted to provide a clear visualization of the shortcomings associated with each definition and classification. Hence, this review article is an attempt to highlight the main points as well as shortcomings in terminology, definitions, clinical classifications and histopathologic gradings which have been associated with leukoplakia till date.

Keywords: Leukoplakia; Dysplasia; Definitions; Classifications; Grading

Introduction

The term "*leuko*" refers to white and "*plakia*" signifies a plaque/patch. Hence, the literal meaning of the term leukoplakia is a "white plaque". More than any other oral disease, leukoplakia has suffered from an excess of diagnostic terms and definitions; at least 75 have been used thus far. This has led to such mystification that many clinicians refuse to use any term beyond "white patch" [1]. The first recorded white oral plaque/patch was an "ichthyosis" reported in 1818 by Alibert of Paris [2].

Although innumerous definitions and classifications have been devised, still there is a lack of consensus. The aim of this paper is to enlighten the highlights and shortcomings of these definitions and classifications. The knowledge and understanding of all the terminologies and classifications along with their shortcomings will provide a better insight for evaluating their appropriateness and comprehensiveness.

Terminologies and definitions

The first definitive terminology associated with leukoplakia was given by Schwimmer in 1877 [3]. Since then, numerous changes have been introduced by authors pertaining to size, etiology, exclusion of other lesions and potential for malignant transformation. The highlights, new points and shortcomings associated with each terminology have been consolidated in Table 1 [4-10].

Clinical classifications

Leukoplakia is one of the most commonly encountered white lesions by the clinicians and still holds an enigma around itself. Proper identification of the type of leukoplakia holds the key to successful treatment of the lesion. Hence, it is important for the clinician to recognize the type of leukoplakia as it can help in planning the treatment and also in predicting the malignant potential of the lesion [11].

Till date, numerous classifications for leukoplakia have been introduced based on criteria such as etiology, appearance, size and presence or absence of dysplastic features. Some authors have even commented, the clinical appearance of leukoplakia can be used to suspect the possibility of dysplasia being present in a lesion. Pindborg, et al. [12] confirmed that speckled leukoplakia was often associated with epithelial dysplasia or carcinoma as compared to homogenous leukoplakia. Sugar and Banoczy [13] in their three tiered clinical classification of 1969, reported that leukoplakia erosiva and leukoplakia verrucosa were more often associated with epithelial dysplasia than leukoplakia simplex. However, the clinical appearance cannot be confirmatively associated with presence or absence of dysplastic features. Various clinical classifications used for leukoplakia and their basis have been consolidated in Table 2 [14-17].

Histopathologic grading

Although leukoplakia is a pure clinical term and the lesion has no specific histology *i.e.* it may or may not demonstrate dysplasia. However for the purpose of histopathologic reporting, the term "dysplasia" has been used [18]. Various authors have proposed grading systems for leukoplakia, but each system has its own shortcomings. The highlights, new points and shortcomings of these grading systems have been consolidated in Table 3 [19-34].

Table 1: Terminologies and definitions associated with leukoplakia.

Author	Highlights	New Points	Shortcomings
Schwimmer [3] (1877)	First used the term "Leukoplakia" to describe a white lesion	A specific terminology introduced for white lesions	Was very vague with no description regarding non-scrapability/ dissimilarity to other diseases
WHO sponsored meeting of investigators on Oral Precancerous conditions at Copenhagen [4] (1967)	A raised white patch of the oral mucosa measuring 5mm or more, which cannot be scraped off and which cannot be attributed to any other diagnosable disease	Size criterion introduced	No mention of etiologic factors
Pindborg [5] (1972)	A white patch or plaque on the mucous membrane that cannot be removed by rubbing and cannot be classified as any other diagnosable disease	Removed the size criterion	No mention of etiologic factors
WHO collaborating centre for Oral Precancerous lesions [6] (1978)	A white patch or plaque that cannot be characterized clinically or pathologically as any other disease	*Emphasized on absence of histological connotation *Only terminology to emphasize on clinical exclusion of other white lesions	*Subjective as lesions like leukoedema created a problem *Biopsy required to give diagnosis *No emphasis on associated etiology
First International Conference on oral leukoplakia held at Malmo, Sweden. Axell et al. [7] (1984)	A white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except use of tobacco	*Tobacco was clearly stated as the etiology *Proposals for etiological and clinical description of leukoplakia	*Association with causative agents is difficult to assess *Several tobacco induced lesions are partly white but are not traditionally described as leukoplakias
Bouquot JE [8] (1994)	A chronic white mucosal macule which cannot be scraped off, cannot be given another specific diagnostic name and does not typically disappear with removal of known etiologic factors	*Diagnostic definition *First definition in which leukoplakia was mentioned as a precursor of malignancy	Known etiologic factors not mentioned
International symposium held in Uppsala, Sweden (1994) [9]	A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable disease	Term "predominantly white" helped in excluding lesions like pre leukoplakia and leukoedema which created an issue earlier	No description about the potential for malignant transformation
Axell T et al. [9] (1996)	A predominantly white lesion of oral mucosa that cannot be characterized as any other definable lesion clinically or pathologically, often associated with tobacco products, some of which will transform into cancer	Emphasized that some oral leukoplakias will transform into cancer	
Warnakulasuriya S et al. [10] (2007)	A white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk of cancer		*Consideration should be given to reintroduce size and scrapability as a criterion *It was very vague and nothing new was introduced

Table 2: Clinical classifications of leukoplakia.

Author	Based On	Clinical Types	Remarks
Mehta et al. [14] (1971)	Clinical appearance	*Homogeneous – A raised plaque of variable size which is predominantly white but can be grayish or yellow *Ulcerated – Red/yellowish area surrounded by white patches which appears like an ulcer *Nodular – A white patch on an erythematous base	* It was the first attempt to clinically categorize leukoplakia * It was clinically applicable
Pindborg et al. [5] (1972)	Clinical appearance	*Ebbing tide – Appears like indulations left on sand by an ebbing tide. Especially occurs on floor of the mouth *Others– All other types of appearances were grouped together	*Inconclusive *Not commonly used
Amagasa et al. [15] (1977)	Clinical appearance	*Type 1- Flat white patch/plaque without red components *Type 2- Flat white patch/plaque with erosion or red components *Type 3- Slightly raised or elevated white patch/plaque *Type 4- Markedly raised or elevated white patch/plaque	Introduced the criteria of being flat or raised

Banoczy J [13] (1982)	Clinical appearance	*Leukoplakia Simplex - White homogeneous keratinized lesion, slightly elevated *Leukoplakia verrucosa - White verrucous lesion with wrinkled surface *Leukoplakia erosiva - White lesion with erythematous, erosion, fissures	For the first time verrucous lesions were mentioned separately
Axell et al. [9] (1984)	Etiology	*Idiopathic - Etiology unknown *Tobacco associated leukoplakia – Caused by tobacco	It was difficult to apply clinically
International symposium held in Uppsala, Sweden [9] (1994)	Clinical appearance	*Homogenous – Predominantly white with cracked/wrinkled/smooth surface but a consistent texture throughout. *Non-homogenous Leukoplakia – Erythroleukoplakias – Red and white lesion Nodular – slightly raised, rounded, red and/or white excrescences Exophytic – irregular blunt or sharp projections	Clubbed nodular and ulcerative together
Schepman [16] (1995)	Size (L), Site (S), Clinical aspect (C) and Histo-pathological features (P)	Provisional (Clinical) Diagnosis 1st symbol: L = Extent of leukoplakia L0 = No evidence of lesion; L1= Lesion<2 cm; L2 = Lesion >2cm to 4 cm; L3 = Lesion >4 cm; Lx = Not specified 2nd symbol: S= Site of leukoplakia S1 = All oral sites except for floor of mouth & tongue (Low Risk Sites); S2 = Floor of mouth and / or the tongue (High Risk Sites); Sx = Not specified 3rd symbol: C = clinical Aspect C1= Homogenous; C2= Non-homogenous;C3= Not specified Definitive (Histopathological) diagnosis 4th symbol: P = Histopathological features P1 = No dysplasia; P2 = Mild dysplasia; P3 = Moderate dysplasia; P4 = Severe dysplasia; Px = Not specified Proposal for staging system for Oral leukoplakia Stage I = Any L, S1, C1, P1 or P2 Stage II = Any L, S1, C2, P1 or P2 Any L, S2, C2, P1 or P2 Stage III = Any L, S2, C2, P1 or P2 Stage IV = Any L, any S, any C, P3 or P4	*It gave detailed description in terms of size, site and clinical aspect like TNM staging * It was time consuming to use
Waal et al. [17] (2000)	Size & pathology of leukoplakia, focusing on absence or presence of epithelial dysplasia.	Symbol: L = Size of leukoplakia L1 = Size of single or multiple leukoplakia together < 2 cm; L2 = Size of single or multiple leukoplakia together 2-4 cm; L3 = Size of single or multiple leukoplakia together >4 cm; LX = Size not specified. Symbol: P = Pathology P0= No epithelial dysplasia (includes no or perhaps mild epithelial dysplasia); P1= Distinct epithelial dysplasia (includes mild to moderate to possibly severe epithelial dysplasia.); PX= Absence of epithelial dysplasia is not specified in pathology report. Staging system proposed was- Stage I = L1P0 Stage II =L2P0 Stage III = L3P0 or L1L2P1 Stage IV = L3P1	* It was a simplified version of classification proposed by Schepman * It was less time consuming as compared to classification given by Schepman

Table 3: Histopathologic grading systems associated with leukoplakia.

AUTHOR	HIGHLIGHTS	NEW POINTS	SHORTCOMINGS
Smith and Pindborg system [19] (1969)	*Attempted to standardize grading of dysplasia by photographic method * 13 histological features were standardized by a set of photographs *Each feature was graded as absent, slight or marked *Dysplasia was graded as absent, mild, moderate and severe	Produces an assessment of dysplasia on an ordinal scale which facilitates statistical analysis	* Numerical scores for individual features have been allocated subjectively by the authors and are not evidence-based *It suffers interobserver and intraobserver variability * Time-consuming to use
Banoczy and Sciba [20] (1976)	* Epithelial dysplasia was diagnosed using 9 dysplastic features suggested by Mehta et al (1971). * Graded epithelial dysplasia as mild, moderate and severe	Dysplasia was graded on basis of number of dysplastic features. Mild = 2 dysplastic features. Moderate = 2 to 4 Severe = 5 or more	* Was based on subjective interpretation of the features * Didn't take into account which factor was important in determining the malignant potential

W.H.O.[21] (1978)	* Listed 12 histologic features that characterized epithelial dysplasia * Dysplasia was again graded as mild, moderate and severe	Grading was based on the thickness of epithelium involved, nuclear abnormalities, cell maturation and stratification and abnormal mitosis. Following new dysplastic features were added: 1. Drop shaped rete ridges 2. Mitotic figures in superficial layers of epithelium 3. Enlarged nucleoli	* It suffers interobserver and intraobserver variability * Didn't take into account which factor was important in determining the malignant potential
Kramer [22] (1980)	*Listed 14 dysplastic features *Epithelium was called dysplastic if it showed presence of 2 or more of the dysplastic features *Dysplasia was graded as present or absent	*Grading was based on the same criteria as that of WHO (1978) *Following new dysplastic features were added: 1.Cell crowding 2.Abnormal mitosis	* It suffers interobserver and intraobserver variability * Didn't take into account which factor was important in determining the malignant potential
Burkhardt and Maerkar [23-25] (1981)	Listed 6 histological and cytological parameters, based on which diagnosis and classification of epithelial dysplasia could be made. Dysplasia was graded as low, medium, high and Carcinoma in situ (CIS)	*A new category i.e. CIS was introduced * Introduced additional indicators of dysplasia like increase in subepithelial lymphocytes, plasma cells and interepithelial cells (stroma reaction) and presence of candida organisms.	
Lumermann H. et al. [26] (1995)	Considered basal cell hyperplasia, nuclear enlargement and hyperchromaticity, drop shaped rete pegs as 'minimal' criteria for diagnosis of oral epithelial dysplasia. Dysplasia was graded as mild, moderate, severe, CIS, Verrucous hyperplasia with dysplasia	*Grading was based on thickness of epithelium involved by minimal criteria of diagnosis *A new category i.e Verrucous hyperplasia with dysplasia was introduced	* The new category (verrucous hyperplasia) creates confusion during grading
Neville et al. [27] (1995)	Graded dysplasia as mild, moderate, severe, CIS		
Speight P M et al. [28] (1996)	Graded dysplasia as mild, moderate, severe	Considered the thickness (height) to which the cellular and tissue changes may extend, as important in grading dysplasia	Warnakulasuria (2001) commented that there was wide variation in the thickness of the covering epithelium in the oral cavity, with much undulation which lead to practical difficulties in using this grading system [29]
Kuffer and Lombardi [30] (2002)	*Proposed to dismember the classical "oral precancerous lesions" into following categories: Risk lesions - which histologically do not show dysplasia (eg. Simple tobacco keratosis) Precursors of SCC-lesions with dysplasia (i.e. already engaged in the process of malignant transformation (eg; tobacco keratosis with dysplasia)	Introduced the terms risk lesions and precursors of SCC (squamous cell carcinoma)	*Using the term "risk lesion" for lesions without dysplasia which have a no risk of Malignant transformation (eg. Frictional keratosis) is inappropriate. *All dysplasias do not progress to SCC, hence calling all dysplasias as precursors of SCC is not justified.
Brothwell D J et al. [31] (2003)	Graded epithelial dysplastic lesions according to 5 point scale; 0 = No dysplasia;1 = Mild;2 = Moderate;3 = Severe;4 = CIS	Using this system, and statistical analysis, authors proved that intra and interobserver agreement in grading the dysplastic lesions were consistent	
Ljubljana [32] (2003)	*Developed to cater for the special clinical and histological problems of laryngeal abnormalities. *Terms used were– Simple hyperplasia, abnormal hyperplasia, Atypical (risky) hyperplasia, CIS		Still doubtful if this system can be used satisfactorily for oral and oropharyngeal precursor lesions

WHO [33] (2005)	*Grading was based on cytological and architectural dysplastic features listed by WHO in 2005. *Dysplasia was graded as – Squamous hyperplasia, mild, moderate, severe dysplasia, CIS	Squamous hyperplasia introduced as a new category	
Binary system [34] (2005) proposed by Omar Kujan et al.	* Considering the problems in making reliable distinctions between the different grades, 4 grades were collapsed to 2. *Categories were: High risk lesions (with potential susceptibility for malignant transformation) and Low risk lesions (no potential for malignant transformation)	*With the reduction in number of grades, interobserver variability was expected to decrease	

Conclusion

Leukoplakia has been one of the most debatable topics amongst the pathologists owing to its ever changing definitions, terminologies, classifications and interobserver and intraobserver variabilities. Till date, no definition, terminology, classification or grading has been declared to be ideal, and this leads to lack of uniformity in their usage by pathologists around the world. The knowledge and understanding of all the terminologies and classifications along with their shortcomings will provide a better insight for evaluating their appropriateness and comprehensiveness.

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