DOI: 10.7860/JCDR/2022/52294.16219

Review Article

Oncology Section

Characterisation of Clinicopathological and Molecular Features of Leukoplakia not Associated with Tobacco- A Scoping Review

KALPA PANDYA[1], SIVAKUMAR PRADEEP[2], GVV GIRI[3], MALATHI NARASIMHAN[4]

ABSTRACT

Tobacco has been implicated as the strongest risk factor for oral malignancies and common potentially malignant disorders. Recent trend shows an increase in the prevalence of these lesions in non tobacco population. Studies suggest that clinicopathological features of leukoplakia differ in tobacco users and non users. Also, leukoplakia without known risk factors is at a higher risk of malignant transformation. Preliminary studies on carcinogenesis of non tobacco-associated head and neck cancers have identified a difference in the key genes involved in the pathogenesis of cancers associated with and without tobacco. While the genetic characterisation of non tobacco oral cancers is gaining focus in the literature, there is a paucity of studies on non tobacco leukoplakia. An understanding of the non tobacco leukoplakia, possibly a distinct subgroup, may provide an insight into the inception of non tobacco oral cancers, leading to avenues for prevention, early diagnosis and precision medicine-led treatment approaches. Through this narrative review, authors revisit and summarise the existing literature on leukoplakia among non tobacco population.

Keywords: Non smoker, Oral leukoplakia, Potentially malignant disorders

INTRODUCTION

Tobacco has been implicated as the greatest risk factor for cancers and precancers of the oral cavity. With the decline in tobacco consumption, there has been a rise in these conditions in non users of tobacco [1]. Apart from tobacco and alcohol, numerous risk factors have been speculated for oral cancers, none with conclusive evidence. Although an established carcinogen for oropharyngeal cancers, the role of Human Papilloma Virus (HPV) in causing Oral Squamous Cell Carcinoma Cancers (OSCC) is debatable [2]. Preliminary studies on carcinogenesis of Non Tobacco-associated (NT) head and neck carcinomas have identified a difference in the key genes involved in the pathogenesis of cancers associated with and without tobacco [3,4].

Longitudinal studies have shown that most OSCC arise from clinically abnormal oral mucosa, usually a red or white patch [5,6]. More recently, these changes have been associated with field cancerisation, indicating that the rest of the clinically normal mucosa in these patients may harbour molecular changes of potential malignancy. In 2007, the World Health Organisation (WHO) recommended the term 'Oral Potentially Malignant Disorders' (OPMD) for all lesions known to precede oral cancers [Table/Fig-1] [7]. Leukoplakia is the most commonly encountered OPMD, with a worldwide prevalence of about 2.6% [8]. Histologically, it manifests as a spectrum from hyperplasia to mild, to moderate, to severe dysplasia. Although tobacco is the primary risk factor for leukoplakia, significant numbers of these lesions occur in patients without tobacco exposure [9,10].

Some studies have suggested that clinical manifestations of leukoplakia differ in tobacco users and non users. Also, NT leukoplakia is at a higher risk for Malignant Transformation (MT) [11,12]. An understanding of NT leukoplakia may provide an insight into the inception of NT-OSCC. Early detection, diagnosis, and treatment of leukoplakia may contribute to reducing the incidence of OSCC. Tobacco-induced leukoplakia is known to regress after cessation of the habit, reducing its risk of MT; however, this is not achievable in NT leukoplakia [13]. Many studies on NT leukoplakia have been published; however, the data are highly heterogeneous in terms of the clinical definition of leukoplakia, histopathological criteria, and inclusion of other OPMD, making a systematic review of the literature difficult. The review aimed to revisit and summarise the existing literature on NT leukoplakia.

1. Leukoplakia
2. Erythroplakia
3. Oral submucous fibrosis
4. Oral lichen planus
5. Proliferative verrucous leukoplakia
6. Actinic cheilitis/Actinic keratosis
7. Palatal lesions in former smokers
8. Oral lupus erythromatosus
9. Dyskeratosis congenita
10. Oral lichenoid lesions and reactions
11. Oral chronic graft-versus-host disease
12. Chronic hyperplastic candidosis
13. Oral exophytic verrucous hyperplasia

[Table/Fig-1]: Oral Potentially Malignant Disorders (OPMD) as defined by the World Health Organisation (WHO) [7].

LITERATURE SEARCH

A systematic search was performed in PubMed and Cochrane databases with the search terms, "Oral potentially malignant disorder*", "Leukoplakia", "Epithelial dysplasia", "Oral dysplasia", "Precancerous Conditions", "Non Smokers", and "Non tobacco". The search involved observational studies that compared the histopathologically proven leukoplakia in tobacco users with that in non users. References cited in the included studies were further searched for any eligible studies. Authors were also contacted for any unclear data.

CLINICOPATHOLOGICAL FEATURES

The proportion of individuals with NT leukoplakia: The proportions of leukoplakia patients without a history of tobacco use vary greatly among studies. Lima JS et al., analysed 315 patients with leukoplakia, of whom 46% were non smokers [14]. de la Oliva J et al., found similar

results, however, their study involved patients with both leukoplakia and erythroplakia [15]. [Table/Fig-2] summarises the percentages of non smoking patients with leukoplakia across available studies. Several authors have reported the proportions of non smokers in patients with oral dysplasia or OPMD without a clear demarcation of the types of OPMD [14,16-18]. Discrepancies in describing these lesions may compromise comparisons of the results of the studies. Diagnosis of leukoplakia must be made only after the exclusion of a possible local traumatic factor such as a sharp tooth or the presence of a prosthesis. Classifying frictional keratosis as leukoplakia is a common mistake and must be avoided [16].

Author	Country of study	Total number of cases of leukoplakia	Percentage of non smokers
Yagyuu T et al., [18]	Japan	200	70.5%
Tomo S et al., [19]	Brazil	50	5%
Silverman S et al., [20]	USA	257	27%
Freitas MD et al., [16]	Spain	52	21.1%
Wang T et al., [21]	China	875	47.6%

[Table/Fig-2]: Percentages of non tobacco patients across various countries [16,18-21].

Gender predilection for non tobacco-associated leukoplakia: A majority of studies indicated that NT leukoplakia is more prevalent among females [12-14,16,22,23]. Yagyuu T et al., found that 73.7% of non smoking patients with leukoplakia were females [18]. Interestingly, a similar gender predilection has been observed in non tobacco users with OSCC. In their study, Lima JS et al., found that non smoking females were more prone to dysplastic changes in leukoplakia in comparison with men [14].

Age: Most studies support a higher median age, above 60 years, in patients with NT leukoplakia [11-14,17]. Yagyuu T et al., reported a mean age of 66.9 years among non smokers, and Lima JS et al., reported a median age of 63 years among non smoking patients with leukoplakia [14,18]. The reason for the differences in ages between smokers and non smokers is unknown but could be due to environmental exposure to tobacco predisposing some individuals to precancers and cancers.

Clinical characteristics: Yagyuu T et al., found no significant differences in the clinical features or site predilection between smokers and non smokers [18]. Contrary to these findings, Lima JS et al., and Schepman KP et al., have reported the most frequent sites of leukoplakia to be the tongue in non smokers and the floor of the mouth in smokers [14,22]. Freitas MD et al., also observed the tongue to be a common site for the occurrence of leukoplakia in non smokers [16]. In general, leukoplakia on the tongue has been cited as a high-risk feature for MT in both smoking and non smoking patients [24]. Tongue leukoplakia is also regarded as an indication for surgical excision as opposed to conservative management. It is noteworthy that NT OSCC shares many of these clinical findings in NT leukoplakia. The cause for the predilection of the tongue in non smokers with leukoplakia is unknown.

Malignant Transformation (MT) in NT leukoplakia: The absence of tobacco exposure has been regarded as a risk factor for the MT of leukoplakia [12]. Yagyuu T et al., found a higher five-year cumulative MT rate in non smokers than in smokers (9.3% vs 3%) [18]. Rock LD et al., in their study of 455 cases of Oral Epithelial Dysplasia (OED), demonstrated that non smokers had twice the risk of MT compared with smokers. Also, OED in the floor of the mouth of non smokers had a 38-times-higher risk of MT compared with that of smokers [11]. Cerqueira JM et al., and Barfi Qasrdashti A et al., also found a higher MT rate in non smokers [23,24].

MOLECULAR CHANGES IN NON TOBACCO-ASSOCIATED LEUKOPLAKIA

Carcinogenesis is believed to be a process of aggregation of mutations in driver genes, eventually manifesting clinically as cancer. These mutations may be germline mutations, a result of environmental carcinogens, or both. The presence of premalignant and malignant lesions in patients without exposure to a known carcinogen may be due to genetic predisposition or an unidentified risk factor. Several mutational changes have been described in oral leukoplakia [Table/Fig-3] [25]. Few studies have also compared the genetic profiles of individuals with leukoplakia, both with and without a history of tobacco use. de la Oliva J et al., performed a genome-wide analysis of smokers and non smokers with extensive or multifocal leukoplakia and erythroplakia [15]. They studied the copy number changes and imbalances in the alleles through microarrays. The earliest changes noted were similar in both smokers and non smokers, including Loss Of Heterozygosity (LOH) in 9p21p24, 3p14.2, 9q34.11q34.3, and 3p21.1p26.3 cytobands. Zhang L et al., have predicted LOH profiles as the risk predictors for MT in patients with OED. They found that LOH at 3p and/or 9p and loci on 4q/17p increased the risk of MT. This predictor model was found to be similar in both smokers and non smokers [13]. Polymerase chain reaction studies to detect p53 mutations in 26 archival samples found that none of the lesions from those who had never used tobacco harboured the p53 mutation [26]. Further studies using next-generation sequencing and transcriptomics are warranted to identify possible genetic mutations specific to NT-OED.

Molecular changes	Findings
Loss of Heterozygosity (LOH) at 3p and 9p chromosomal locations	Similar in tobacco and non tobacco leukoplakia
TP53 mutation	Less in non tobacco leukoplakia however IHC studies show no significant difference
PDL1 expression	Higher in non tobacco leuokoplakia
C-jun, pC-jun expression	Lower in non tobacco leukoplakia

[Table/Fig-3]: Molecular changes investigated in non tobacco leukoplakia.

Proteins involved in the cell cycle have been studied for diagnosis and treatment of various cancers. Several studies have compared specific molecular markers in tobacco- and NT leukoplakia through immunohistochemistry. In a study by de la Oliva J et al., p53 expression appeared to be similar in smokers and non smokers [15]. Yagyuu T et al., in their study of 200 patients, found a higher expression of PDL1 and elevated numbers of subepithelial CD163+ cells in patients with NT leukoplakia, indicating a difference in the microenvironment of leukoplakia with and without tobacco exposure [18]. C-Jun and pc-Jun are proteins related to cell proliferation and may indicate a worse prognosis. Lima JS et al., showed that the number of cells with c-Jun and pc-jun increased with an increase in the number of cigarettes smoked per day, and the number of c-Jun cells was higher in dysplastic cells of smokers compared with those of non smokers [17].

POSSIBLE RISK FACTORS FOR LEUKOPLAKIA OTHER THAN TOBACCO

A study by Hashibe M et al., found alcohol to be a significant risk factor for oral leukoplakia, especially among non users of tobacco [27]. In contrast, a meta-analysis by Rodriguez-Archilla A and Garcia-Gamez MT found no significant relationship between alcohol and leukoplakia [28]. Alcohol has been established as an independent risk factor for OSCC; however, the role of alcohol in the etiology of leukoplakia is unclear [29]. Larger multicentre observational studies in a non drinking population are required to determine if alcohol is an independent risk factor for leukoplakia [28]. A number of studies have evaluated the role of HPV in leukoplakia [28,30,31]. A meta-analysis of 14 studies showed 5.41 times higher chances of developing leukoplakia in presence of HPV infection [28]. However, HPV may be a co-existent infection rather than an etiological factor [28]. Candida has also been implicated as a risk factor for MT of leukoplakia [31]. Recently, several studies have investigated the association between candida and leukoplakia. A systematic review of

16 studies reported a prevalence of candida infection in leukoplakia patient to be from 6.8-100%. The authors of the systematic review support the theory that candida may promote dysplasia, however they have suggested further studies to establish a definitive role of candida in MT of leukoplakia [32].

Non Tobacco-Associated Leukoplakia of Larynx

Risk factors other than tobacco have been investigated in leukoplakia of the larynx. As with oral leukoplakia, laryngeal precursor lesions histologically manifest as hyperplasia or hyperkeratosis, even severe dysplasia [33]. To date, smoking has been implicated as the most common etiological agent. However, emerging evidence suggests gastrointestinal reflux to have a possible etiological role in this disease [34]. Lu G et al., found acidic laryngopharyngeal reflux as an indication for invasive treatment of vocal fold leukoplakia [35]. A recent study by Chen M et al., through regression analysis, found Helicobacter pyroli to be an independent risk factor for leukoplakia of the larynx [33]. These risk factors deserve attention in their possible role in oral leukoplakia [36].

SCOPE FOR FURTHER RESEARCH

Lung cancers in non smokers have been identified as distinct entity with clinicopathological features, survival and genetic profiles compared to lung cancers in smokers. Higher Epidermal Growth Factor Receptor (EGFR) mutations have been found in non smokers with lung cancer, making them more responsive to EGFR-based targeted therapies such as gefitinib and afatinib [37]. A similar perspective in understanding NT oral cancers and precancers may lead to landmark findings influencing management of these diseases. Although significant evidence has emerged on OSCC in non users of tobacco [38], leukoplakia in non tobacco users have not been studied extensively. Also, due to the rarity of NT leukoplakia, the majority of the studies have taken other OPMD into account along with leukoplakia. Many retrospective studies on archival samples have been done on OED without a clinical correlation. A uniform finding of higher MT in non smokers emphasises the need to further investigate this subset of patients. Multicentre studies with rigid selection criteria and next-generation sequencing technologies may contribute in elucidation of the nature of this disease. Studies to assess other possible risk factors for leukoplakia are warranted.

CONCLUSION(S)

Non tobacco-associated leukoplakia shows a different clinical behaviour and malignant progression compared with that associated with tobacco. The reason for this difference is unknown and may lie in the genetic profile of the two forms. A uniform finding of higher MT in non smokers demands attention for this type of leukoplakia. Demographic and clinical characteristics of NT leukoplakia and non tobacco-associated OSCC display distinct similarities. Thus, an understanding of NT leukoplakia may provide an insight into the inception of NT oral cancers, providing avenues for prevention, early diagnosis, and targeted-therapy-led approaches.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Lecturer, Department of Oral and Maxillofacial Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
2. Junior Consultant, Department of Head and Neck Surgical Oncology, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India.
3. Professor, Department of Oral and Maxillofacial Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
4. Professor, Department of Oral and Maxillofacial Pathology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Kalpa Pandya,
Senior Lecturer, Department of Oral and Maxillofacial Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
E-mail: kalpa.pandya@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 13, 2021
- Manual Googling: Dec 11, 2021
- iThenticate Software: Jan 03, 2022 (3%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 12, 2021**
Date of Peer Review: **Nov 16, 2021**
Date of Acceptance: **Jan 04, 2022**
Date of Publishing: **Apr 01, 2022**