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Precancerous oral lesions: A comprehensive review of the literature

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Abstract

Early diagnosis is crucial for conditions like precancerous or premalignant lesions. Numerous premalignant lesions, such as lichen planus, oral submucous fibrosis, and leukoplakia, can develop into cancer in the oral cavity. Certain risk factors, including alcohol consumption, tobacco use, and chewing tobacco, are significant contributors to the development of potentially cancerous oral diseases. Researchers have long known that apparent clinical alterations in the oral mucosa, typically in the shape of a white or red patch, precede all cases of oral cancer. Early diagnosis of lesions facilitates timely treatment.

Keywords: Diagnosis, premalignant, lesion, oral submucous fibrosis, lichen planus, leukoplakia, management.

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1. Introduction

The word "cancer" is Latinized from the Greek word "karkinos," which means "crab," referring to the way carcinoma reaches its claws into nearby tissues [1]. Globally, oral cancer is the sixth most frequent cancer [2]. A premalignant lesion is a condition, illness, or discovery that has the potential to develop into cancerif left untreated [3]. It is commonly known that there are two stages in the formation of oral mucosal cancer: the first stage involves the presence of a precursor, which later develops into cancer [4]. Researchers have long known that almost all cases of oral cancer are followed by obvious clinical alterations in the oral mucosa, most commonly in the form of a red or white patch (a two-step process of cancer development). The diagnostic delay in recognizing PMDs is thought to be caused by a lack of understanding among health-care practitioners about early detection techniques and a lack of public awareness regarding signs, symptoms, and risk factors [1].The worldwide literature has used a variety of words to refer to clinical manifestations that may eventually develop into cancer, including precancer, premalignant, precursor lesions, intraepithelial neoplasia, and possibly malignant [5]. Oral cancer is more likely to happen in a precancerous lesion—a morphologically changed tissue—than it seems that normal counterpart. A precancerous condition is a broad situation that is linked to a markedly elevated chance of developing cancer. Recently, a general term known as potentially premalignant oral epithelial lesions (PPOELs) has been introduced to describe lesions with malignant potential that are both histologic and clinical. The World Health Organization (WHO) meeting in 2005 approved the name oral potentially malignant condition (OPMDs) [6].

Premalignant lesions should be identified, diagnosed, and treated as soon as possible to avoid developing into oral squamous cell carcinoma (OSCC). Because early identification is directly connected with stage de-escalation at initial presentation, it is essential to increase the 5-year survival rate [6].

2. Precancerous lesions

On the subcontinent of South Asia, millions of people chew betel. Oral squamous cell carcinoma, oral leukoplakia, and submucous fibrosis are linked to betel usage. Leukoplakia has also been linked to persistent friction, alcohol, tobacco, and other factors [5]. Oral cancer risk factors include a variety of precancerous abnormalities.

2.1. Oral Submucous Fibrosis (OSF)

It is commonly known that OSF has the potential to be cancerous. This illness is quite uncommon in western nations and primarily affects Indians. Juxta-epithelial fibrosis, or fibrosis of the lining mucosa of the upper digestive tract, affects the oral cavity, oropharynx, and often the upper third of the esophagus. Oral submucous fibrosis (OSF) is a chronic and potentially malignant condition. The typical clinical picture, with the exception of early stages of the disease, is brought on by lamina propria and submucosa fibrosis and a progressive decrease in tissue mobility. Distinct populations may exhibit varying oral locations of participation [5]. A juxta-epithelial inflammatory response results in fibroelastic alteration of the lamina propria and epithelial atrophy, which in turn causes the oral mucosa to stiffen and develop trismus. Speech, mastication, swallowing, and oral hygiene can all be impacted by trismus. As mouth opening is restricted in the early stages of the condition, the most typical symptoms are a burning sensation and/or sensitivity to spicy food. It usually strikes in the second or third decade, and it can impact people of both sexes [7].Its etiology is unclear and is assumed to be complex [7].Theprimary ingredient in betel quid, areca nut chewing, is especially linked to OSF. Chewing areca nuts, eating chilies, immunological and genetic processes, eating too little, and other factors have all been linked to the development of OSF. It has been discovered that patients with OSF have higher frequencies of HLAA10, HLA-B7, and HLA-DR3 [8].For the treatment of OSF, a variety of medicinal interventions, such as vitamin supplements, antioxidants, and herbal medications, have been attempted [5].

2.2. Oral lichen planus (OLP)

OLP is a long-term, inflammatory, autoimmune condition that can affect the scalp, nails, oral and vaginal mucosa, and skin. Keratinocyte cell loss sets off an unchecked immunological response that results in a build-up of CD8+ T lymphocytes in the basal membrane. While OLP is thought to be an autoimmune illness driven by T cells, its origin is mostly unknown and most likely complex [7].

2.3. Leukoplakia

It is a non-scrapablelesion. Schwimmer used the word "leukoplakia" in 1877 to refer to a white tongue lesion that was most likely syphilitic glossitis. It is the most researched PMD and the most prevalent premalignant lesion (85%). Leukoplakia is described as "A white patch or plaque that cannot be characterized clinically or pathologically as any other disease" by the WHO working group. As a result, the disease's diagnosis is established by an exclusion procedure [5]. The range of the overall OL prevalence rate was 1% to 5% [6].The most well-known precursor lesion is oral leukoplakia. How many oral squamous cell carcinomas grow from precursor lesions and how many from what seems to be normal oral mucosa is unknown. No particular clinical appearance is linked to oral epithelial dysplasia.Aleukoplakia biopsy performed on the floor of the mouth revealed significant dysplasia and cancer in situ [4].The oral cavity is known to develop leukoplakia's in practically every location. Lesions in the lower lip, lateral tongue, and floor of the mouth are more prone to exhibit malignant or dysplastic alterations. Leukoplakia's' potential to becoming malignant depends on a number of variables [5]. Leukoplakia prevalence rates have been recorded in the past to range from 0.4 to 1.59%, with older males showing greater rates [7].There are two forms of leukoplakia's: homogeneous and non-homogeneous (sometimes called "speckled") varieties, which are further differentiated. Proliferative verrucous leukoplakia is an extremely aggressive kind of lesion that almost always progresses to cancer [4]. Proliferative verrucous leukoplakia falls under the non-homogenous category and is a less common variety of leukoplakia. Tobacco affects the oral mucosa's epithelium histologically, which can result in thickening and increased pigmentation [7].

2.3.1. Homogenous leukoplakia

The most frequent are homogeneously white plaques that are seen in the buccal mucosa and typically have little chance of developing into cancer.

2.3.2. Non-homogenous leukoplakia

It could be verrucous or speckled leukoplakia, which is more likely to become malignant than homogeneous leukoplakia. On an erythematous base, speckled leukoplakia is composed of tiny nodules or white flecks. Leukoplakia and erythroblastic may coexist in these lesions, or they may represent a transition between them [4-5].Proliferative verrucous leukoplakia is a heterogenous leukoplakia type having 87% of malignant transformation rate.

2.4. Erythroplakia

Oral erythroplakia (OE) is a diagnostic of exclusion that is visually explained as a crimson, velvety plaque or patch that cannot be linked to any other pathophysiologic disease [6]. Erythroplakia was defined as "any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterized clinically or pathologically as any other recognizable condition" in order to support research on oral precancer. Erythroplakia is far more likely to exhibit dysplasia or cancer even though it is not nearly as frequent as leukoplakia [5]. In pre-malignant lesions, epithelial dysplasia is widely acknowledged as one of the most significant indicators of malignant development [4].The absence of a patch lesion and a flat or even depressed erythematous alteration of the mucosa characterize the clinical presentation. A lesion with both red and white alterations is called "erythroleukoplakia."

The soft palate, ventral tongue, and floor of the mouth are the areas where erythroplakia lesions are most frequently found. While most occurrences are asymptomatic, they can manifest as discomfort or a burning feeling [7].

2.5. Oral Epithelial Dysplasia

It is commonly known that oral epithelial dysplasia (OED) is a common precursor to oral squamous cell carcinoma (OSCC). Based on a histological diagnosis, the World Health Organization (WHO) defines oral dysplasia as a precancerous lesion of stratified squamous epithelium, marked by cellular atypia and lack of normal maturation and stratification, short of carcinoma in situ [6].

2.6. Nicotine Stomatitis

Because of the intense heat produced by the pipestem, nicotine stomatitis—a thickened, hyperkeratotic modification of the palatal mucosa—is most commonly associated with pipe smoking. The palatal mucosa thickens, becomes hyperkeratotic, and sporadically the surface becomes fissured. Popular elevations with red centers appear on the surface frequently; they are the swollen apertures of the little salivary gland ducts. The phrase "nicotine stomatitis" is actually misleading because the alterations are brought on by the extreme heat that smoking produces, not the nicotine itself [5].

2.7. Palatal Lesions in Reverse Smokers

Reverse smoking, when the lit end of a cigarette or cigar is inserted in the mouth, is a custom among some people in Southeast Asian and South American countries. Reverse smoker's palate, a more severe heat-related modification of the palatal mucosa caused by this habit, has been linked to a considerable risk of malignant transformation [5,9].

2.8. Actinic Keratosis

Actinic keratosis, which can develop on the lips among other places, is thought to be a potentially cancerous condition. It is frequently linked to sun exposure. The typical annual progression rate from actinic keratosis to invasive carcinoma is between 0.025 and 16% [10].

2.9. Tobacco Pouch Keratosis

The use of smokeless tobacco, such as snuff or chewing tobacco, is linked to another distinct tobacco-related change of the oral mucosa. These lesions can spread to the nearby gingiva and buccal mucosa, although they usually appear in the buccal or labial vestibule where the tobacco is stored.Whenthe tissues are stretched, any little wrinkles that may have appeared in the early lesions vanish. Other lesions could show up as granular, hyperkeratotic regions. Zones of the mucosa that are greyish white in advanced lesions show significant thickening [5].

2.10. Hereditary Disorders with Increased Risk

Dyskeratosis congenital (DC) and epidermolysis bullosa are two disorders that may have a higher risk of oral cancer. These are uncommon inherited illnesses. Males are impacted by the majority of X-linked DC cases. Individuals with DC frequently experience white plaques on the dorsal tongue, which might be mistaken for leukoplakia. However, the absence of habits and the young age of the patients may indicate that DC is a hereditary condition. There have been reports of malignant changes inside the white patch areas [5].

3. Etiology

Precancerous lesions of the oral mucosa have an unclear etiology. Certain risk factors, including alcohol consumption, tobacco use, and chewing tobacco, are significant contributors to the development of potentially cancerous oral diseases. Tobacco smoking may be a risk factor for oral leukoplakia, even though tobacco chewing is a significant risk factor for oral submucous fibrosis, oral leukoplakia, and erythroplakia. Drinking alcohol may raise the risk of oral leukoplakia by 1.5 times [7].

4. Diagnosis of precancerous lesion

There aren't any trustworthy and approved in vivo chairside adjuncts available yet. As a result, diagnostic adjuncts should only be used in conjunction with tissue biopsies and physical examinations, which are still regarded as the gold standards for diagnosis and detection [11]. The diagnosis is primarily subjective, as some lesions exhibiting dysplasia may not progress to malignancy and some may even regress, whereas lesions in which epithelial dysplasia was not identified in prior biopsies may evolve into carcinoma [4]. A conclusive diagnosis requires microscopic and radiographic pictures of the lesions in addition to clinical findings [12].Lesions associated with other entities, such as lichen planus (which acknowledges that it has the potential to become malignant in and of itself), leukoedema, lupus erythematosus, and white sponge nevus, as well as lesions for which anetiology can be determined, like frictional keratosis and biting of the cheek, lip, or tongue, are excluded as precancerous lesions [4].

4.1. Various methods of diagnosis

4.1.1. Cytopathology

The microscopic examination of cell samples taken from mucosal surfaces by fine-needle aspiration or exfoliative cytology (smears, scrapings, or lavage) is known as cytopathology. The original purpose of exfoliative cytology was to discover cervical cancer cells early. Cyto-brushes are used in exfoliative cytology procedures to produce high-quality smears that contain cells from deeper layers of the epithelium [2]. Using a specialized brush, the oral CDx Brush test device gathers transepithelial cellular samples made up of clusters and free cells. These samples are put on a glass plate and transported to a lab where they undergo staining (using a modified Papanicolaou test), scanning, and microscopic analysis using an imaging system that is computer-based and can classify cells according to how aberrant their morphology is. The computerized results are interpreted by a cytopathologist. "Negative or benign," "positive," or "atypical" results are reported [5].

4.1.2. Brush cytology

When diagnosing oral squamous cell carcinoma in clinically suspected lesions, brush cytology with PAP grading and AgNOR analysis can be employed as an early diagnostic tool, particularly for individuals from lower socioeconomic backgrounds who present with advanced stages [13].

4.1.3. Cytomorphometry

Computer-Aided Analysis Brush Biopsy: Computer-aided analysis and cytomorphometry Brush biopsy is a technique used in the analysis of cellular samples obtained by brush biopsy (Oral CDx Laboratories, Suffern, N.Y.) [2].

- **Vital Iodine Stain-** Prior to biopsy and resection, vital iodine stain (3% Lugol solution) can be applied, and it helps identify the ideal incision site [2].
- ***ChemiluminescenceTechnique/ Chemiluminescence Light-***. The USA approved the chemiluminescence technology (ViziLite, Zila Pharmaceuticals, Phoenix, Arizona) in 2002. Enhancing the detection, visibility, and tracking of oral precancerous lesions is its intended use [2].
- ***Vital tissue staining***with Tolonium chloride (TB)- It is a metachromatic vital dye that may bind more strongly to areas of DNA alteration linked to oral PMD, or it may bind preferentially to tissues experiencing fast cell division (such as inflammatory, regenerative, and neoplastic tissue). Abnormal tissue is stained as a result of the binding, whereas the surrounding normal mucosa remains uncolored. Twelve investigations between 1964 and 1984 were compiled in a meta-analysis, which found an overall sensitivity of 93.5 percent and specificity of 73.3 percent.
- ***Visualization adjuncts***- They operate on the premise that mucosal tissues that are undergoing aberrant changes in metabolism or structure exhibit distinct profiles of absorbance and reflectance when they are subjected to different kinds of light or energy [5].

4.2. Diagnostic markers

4.2.1. Markers

Epithelial differentiation markers and, more recently, genetic markers have emerged as promising candidates to enhance the prognostic assessment of oral cancer precursors. Genetic instability and DNA aberration can be roughly measured by looking at a cell's DNA content, or DNA ploidy [4].

4.2.2. loss of heterozygosity

Loss of heterozygosity (LOH) is the term used to describe the loss of genomic material in one of two chromosomes [4].

4.2.3. P53

It is possible that the most frequent genetic alteration in human cancers is a mutation of the p53 tumour suppressor gene [4].

4.3. Differentiation Markers

4.3.1. Cell-surface carbohydrates

In human tissues, blood group antigen-active cell-surface carbohydrates are widely dispersed. For blood group antigens found on cells other than erythrocytes, the term "histo-blood group antigens" has been proposed. In oral squamous epithelium, histo-blood group antigens of the Lewis, ABH, and T/Tn systems are seen on the surfaces of epithelial cells [4].

5. Prevention

Optimally, the most effective and first approach for managing premalignancy is primary prevention. The greatest way to prevent cancer is topractice yoga, lead a healthy lifestyle, abstain from tobacco use, and avoid smoking. The ultimate objective is to stop premalignancy from becoming malignant. It is highlighted that the time it takes for a lesion to become malignant can range from months to years and is unpredictable. Patients should have long-term follow-up if they have a history of dysplastic or premalignant lesions [6].

6. Management

For leukoplakia, conservative surgical excision is still the preferred course of treatment. Leukoplakia removal hasn't, however, been demonstrated to slow the rate of malignant transformation. The rate of malignant transformation did not appear to differ significantly between patients who underwent any sort of surgical intervention. Disparities in recurrence rates were shown in a study comparing CO_2 laser, NdYAG laser, and KTP laser treatments [5].Depending on the level of clinical involvement, people with OSMF will receive different treatments. If the illness is discovered relatively early on, quitting the habit will be sufficient. The majority of OSMF patients have moderate-to-severe, irreversible disease when they first arrive. Hyaluronidase, IFN-gamma, placental extracts, steroids, and other medications are used in symptomatic treatment to improve mouth movements [7].Every leukoplakic lesion needs to be biopsied. Excisional biopsy is typically suitable for tiny regions of leukoplakia. Antioxidants such as beta-carotene, beta-copene, vitamin A, fenretinide, bleomycin, L-ascorbic acid (vitamin C), and beta-tocoferol (vitamin E) are used in the pharmacological management of leukoplakia. Based on a clinical evaluation, carbon dioxide laser treatment and photodynamic therapy (PDT) may be employed as alternatives to surgery [7].Leukoplakia and erythroplakia are treated quite similarly. Bleomycin, retinoids, and vitamin A are non-surgical therapies. Treatment methods may include surgical procedures such as laser surgery. The course of treatment for OLP depends on how it manifests clinically and whether symptoms are present [7]. Aloe vera, triamcinolone acetonide, and amlexanox were found to be beneficial in the treatment of OLP patients by Kaur et al., (2024) [14].In a tertiary hospital in Odisha, Jamuda et al., (2023) assessed undergraduate dental students' awareness of oral cancer by evaluating their knowledge, attitudes, and practices regarding pre-cancerous lesions and early detection. They came to the conclusion that there is

insufficient information, attitude, and practice at the moment [15].

According to Abdulrahman's systematic review, noninvasive, easily implemented, and highly accurate alternative screening techniques meet the specified standards for being taken into consideration as a competitive alternative to histopathology [16].Torabi et al., (2021) assessed the congruence between the clinical and pathological aspects of Oral Squamous Cell Carcinoma (OSCC) and other oral potentially malignant illnesses. They came to the conclusion that OSCC had the highest level of clinical conformity with histology. Dentists should be aware of oral conditions that have the potential to become cancer in order to diagnose them early and stop the disease from progressing [12]. The importance of focused public health interventions to combat tobacco consumption and raise oral health awareness has been highlighted by systematic research by Gupta et al., (2023) particularly in groups with high prevalence of tobacco use. Global oral health outcomes may be improved more effectively if methods were standardized and varied groups were included in future studies, as this would strengthen the body of evidence [17].

7. Conclusions

Premalignant lesion care is complicated, and there is conflicting information in the literature right now about the best course of treatment. The complex interaction between the environment and the host is responsible for the transformation from normal mucosa to premalignant or dysplastic mucosa and ultimately to malignant alteration. The early diagnosis and treatment of these lesions reduces the risk of cancer, but requires a comprehensive clinical and histological investigation.

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