A Consultant Histopathological Correlation Representation of Oral Potential Malignant Disorder

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ABSTRACT
Oral squamous cell carcinoma (OSCC) represents in any event 90% of every oral threat. It shows huge mortality and bleakness rates. Essentially, all oral malignant growths display a two-venture cycle of disease movement, i.e., an underlying precancerous stage that accordingly develops into definite phase of oral malignancy. The precancerous stages alluded to as possibly harmful issues of oral depression to be specific the leukoplakia, oral lichen planus, erythroplakia, and oral submucous fibrosis.The early detection and treatment aid in an improved prognosis of cancer and is only possible with a proper knowledge of their clinical and histopathological features. Therefore, this mini review we aim to elaborate these features of PMD which will assist in early diagnosis and timely treatment.
KEYWORDS: OSCC; Potentially Malignant Disorders (PMDs),bone marrow failure (BMF)

INTRODUCTION

Oral cancer is a potentially fatal disease typicallysignifies late leading to poor prognosis. The very natural OSCCthat affects many people around world and signifies higher than 90% of head and neck cancers. Recent studies show that 4-10% of cases are reported in patients below 40 years age. Around two thirds of such OSCCs seem to be diagnosed only at its progressive stages. The late identification of many OSCCs is attributed to the delay in patient treatment seeking, lack of patient awareness [1].

Despite the diverse treatment modalities for OSCCs, 5 year survival rate has not enhanced in latest years. OSCCs might arise from PMDs, a termthatislatelypresented by WHO to be used instead of premalignant or precancerous lesions/conditions.PMDs mainly constitute leukoplakia, erythroplakia, erythroleukoplakia, lichen planus, submucous fibrosis and actinic cheilitis. Hence, there is a vital need to detect OPMDs at an early stage. On literature analysis, in indexed journals in English literature for past twenty years very few review articles are available which provide histopathology of different PMDs under one roof which we aim to bring to literature by thisreview [2].

Oral potentially malignantdisorders

PMD is the latest WHO recommended term for set of disorders, which that carry an unpredictable risk of malignant transformation. Examples of white, predominantly white or red disorders of oral mucosa that carry an enhanced risk for oral cancer development are leukoplakia, erythroplakia, submucous fibrosis, erythroleukoplakia, oral lichen planus, actinic cheilitis, dyskeratosiscongenita, xerodermapigmentosusm, epidermolysisbullosa, DLE and Fanconi anemia. Leukoplakia and erythroplakia are very common lesions [3].

Oralleukoplakia (OL)

The termLeukoplakia is given by a Hungarian dermatologist, Schwimmer in 1977. The OL is depicted as white plaque of questionable risk having excluded recognized diseases or disorders that carry no enhancedrisk for cancer. OL is very normal PMDaffecting 0.2- 4.9% of world populace [4]. The most common site affected by OLs varies in different studies and this variation may similarly be related to geographical differences, race, and individual habits. The alveolar mucosa, buccal mucosa, and lower lip were the common sites observed in a study conducted by Waldron and Shafer (1975), while buccal mucosa and the floor of mouth (FOM)arevery usually affected oral sites, followed by lateral border of tongue, with gingiva and labial commissures least affected in a study carried out by Jaber et al (2003).The different classification of OL is tabulated in table 1. The differentiation between them is entirely clinical, based upon surface, color and morphological features.

Staging of OralLeukoplakia

According to "International Classification of Diseases Application to Dentistry and Stomatology (ICD-DA)" codes for oral cavity, three size categories have been proposed, analogous to TNM system of oral cancer [5]. L represents the size of single or multiple leukoplakias as follows:

Size:

L1 < 2 cm L2 =2-4 cm

L3 > 4 cm

Lx size not specified.

P represents the pathology of leukoplakias as follows:

P0 No epithelial dysplasia

P1 Mild or moderate dysplasia

P2 Severe dysplasia

Pxpresence or Absence of dysplasia not specified

Accordingly, four stages have been proposed in this system which includes:

StageI L1P0

StageIIL2 P0

StageIIIL3 P0 or L1 L2 P1 StageIVL3 P1 or anyLP2

Variants of OralLeukoplakia

The "Proliferative verrucous leukoplakia (PVL)" initially introduced by Hansen et al. (1985), more prevalent among elderly women with or without history of tobacco use.Clinically, PVL mostly appears as a flat white keratotic lesion withverrucous surface and may be associated with an erythematous component. As lesion progresses it becomes more exophytic, granular and verruciform ultimately becoming multifocal and developing a warty-type appearance [6].

Candidal Leukoplakia

A secondary candida infection of the epithelium is found in about 10% of all leukoplakias. If the degree of dysplasia is also taken into account, the incidence of candidiasis increases with the degree of dysplasia reaching 38% in lesions showing a high degree of dysplasia. Fungal growth in leukoplakic lesions must therefore be regarded both as a risk factor and as a risk indicator [7].

Epithelial dysplasia in OralLeukoplakia

Leukoplakia without or with mild dysplasia:

With this form of leukoplakia, whitish atrophy of the mucosa is due to increased keratinization (hyperkeratosis) at the surface and thickening of prickle cell layer (acanthosis) beneath. Mucosal keratinization may take the form of anucleate horny squames. (orthokeratosis) or of remnants of nuclei persisting in the keratinocytes (parakeratosis). Less common features are cells swollen with intracellular water or edematous enlargement of intracellular spaces. This group of harmless leukoplakias is not to be considered precancerous and accounts for 74% of oralleukoplakias.

Leukoplakia with moderate dysplasia:

These hold an intermediate position having more marked dysplasia and represent 17%of leukoplakias. Their behavior corresponds largely to that of the group with low-degreedysplasia [8].

Leukoplakia with severe dysplasia &carcinoma insitu:

Leukoplakias with high degree of dysplasia should be considered precancerous. They are detected by the fact that all criteria of dysplasia are usually exist in marked degree. Endophytic growth with downward extension of epithelial rete pegs is a common finding. It might be regarded as an early form of oral cancer not showing invasive growth. 6% of leukoplakias show signs of extreme dysplasia, 3% of leukoplakias show carcinoma in situ.

Oralerythroplakia (OE)

The current widely accepted WHO definition of OE is fiery red patch, which might not be categorizedpathologically or clinicallyas any other definable disease.Previous studies have shown a prevalence range between 0.02% and 0.83%from research performed in South and Southeast Asia. OE is a rare disorder and is much less common than leukoplakia. It is a disease of middle age and elderly and more common in men.Clinically, erythroplakias may have flat or depressed surfaces which may be smooth, granular or nodular with a well-defined demarcation adjacent to mucosa of normal appearance. Erythroplakia tends to present as solitary lesions and rarely affects widespread areas [9].

Histopathology

Erythroplakia as a clinical term does not carry any histological connotation; however, histological biopsy of OE may show epithelial dysplasia, CIS or invasive carcinoma. Although OE is rare, its malignant transformation rate is highest between all of the oral PMDs. Dysplasia and CIS or invasive carcinoma might be seen in more than 90% of OE cases [10].

Oral lichenplanus (OLP)

The OLP is a chronic inflammatory disorder of unknown etiology affecting up to 2% of the middle aged and elderly.It is a cell mediated autoimmune condition associatedwith accumulation of an inflammatory infiltrate composed predominantly of T- lymphocytes below epithelium of oral mucosa which results in cell-mediated damage to basalkeratinocytes.Clinically, OLP has 6 types: papular, reticular, plaque-like, atrophic, and erosive (ulcerative) and bullous. It has characteristic clinical and histological appearancewhich usually allows distinction from OL. [11].

Histologicalfeatures

Hyperparakeratosis with thickening of granular layer, acanthosis with intracellular edema of spinous cells in certain cases, improvement of saw toothpresence of rete stakes are normal highlights. Degeneration of basal keratinocytes and disturbance of securing components of epithelial cellar layer and basal keratinocytes debilitates the epithelial-connective tissue interface. Subsequently, histologic clefts (for example Max-Joseph spaces) might frame, and rankles on oral mucosa might be seen at clinical assessment [12].

LichenoidDysplasia

When dysplasia is seen in epithelium which otherwise has the microscopic features of lichen planus, the lichen planus features are essentially ignored and lesion is graded according to the criteria of epithelial dysplasia, although the term lichenoid dysplasia may be applied to the case. Lichenoid dysplasia is a precancerous condition having lichenoid characteristics. It has just a superficial resemblance to lichen planus and other lichenoid disorders. Clinically and histopathologically, it appears to be lichen planus [13].

Eisenberg histopathological criteria for OLP& Oral Lichenoid Lesion

Essential feature

- Normal epithelial maturation pattern
- Basal cellliquefaction

- **Other nonrequisitefeatures**
- Spindly reteridges, candle-dripping
- Civattebodies
- Parakeratosis
- Ragged division of epithelium from lamina propriabecauseofbasal celldestruction

- **Topographicfeatures**
- droplet-shaped rete, Blunted ridges
- Nonappearance of basal cellliquefaction
- Stratificationdisarray [14]

- **Lichenoidinfiltrate**
- Heterogeneouspopulace
- Perivascular infiltration
- (Deeper) submucosal extension of infiltrate beyond superficial stroma

Oral submucousfibrosis(OSF)

OSF was first portrayed thirty years back by Pindborg and Sirsat. It is viewed as a pre-harmful condition. It is portrayed by a juxtaepithelial fiery response followed by fibroelasticvariation in lamina propria and related epithelial decay. This prompts a confined mouth opening, coming about as lockjaw prompting limitation of food utilization, trouble in keeping up oral wellbeing, just as weakens the capacity to talk. The fibroelastic changes are on the whole because of strange collection of collagen in the sub epithelial layers bringing about thick stringy groups in the mouth [15].

Histopathology

The epithelial changes in the various phases of OSF are prevalently hyperplasia (early) and decay (progressed), related with an expanded inclination for keratinizing metaplasia. The epithelial decay is the checked epithelial change in cutting edge OSF. Injuries including the sense of taste demonstrated prevalently orthokeratosis and those of the buccal mucosa, parakeratosis. The high mitotic include in parakeratotic epithelium, the relationship with parakeratotic leukoplakia and atrophic epithelial changes inclines OSF to harm [16]. Based on the histopathological appearance of recolored (H&E) areas, OSF can be assembled into four obviously determinable stages: early, early, tolerably progressed and progressed. The incendiary cells seen are essentially lymphocytes and plasma cells. The connective tissue in cutting edge stages is described by the submucosal testimony of incredibly thick and avascular collagenous tissues with variable quantities of ongoing incendiary cells.

Actiniccheilitis (AC)

The AC is clinical name for ulcerative sore, now and then with covering development on the mucosa, part or the whole vermilion outskirt of lip.It is an obsessive condition that most habitually influences the vermilion fringe of the lower lip. At the point when both the upper and lower lips are unmistakable, as in bimaxillary projection, the upper lip may likewise be more helpless against daylight introduction. Previously, actinic cheilitis was viewed as being conceivably threatening, with not rare change into intrusive, metastasizing squamous cell carcinoma.The specific mechanism by which AC develops is unknown. Chronic exposure to UV radiation (sunlight) causes mutational alterations in keratinocytes, gradual epithelial deterioration, and inflammatory reactions in the lamina propria, according to the pathophysiology of AC.

Histopathology

Histologically, the squamous epithelium of lip vermilion might show hyperplastic or atrophic changes with confused development, shifting levels of keratinization, cytological atypical and expanded mitotic action with the basic connective tissue indicating basophilic degeneration of collagen and elastosis.Aside from clinical symptoms, biopsy and histological analysis are required in the diagnosis of AC because it is considered a potentially malignant condition, and sun exposure is a risk factor for lip cancer. Using immunohistochemistry techniques, Martnez et al. discovered that the epithelial expression of the p53 and murine double minute (mdm2) genes was dramatically enhanced in AC. Because changes in p53/mdm2/p21 pathway expression are prevalent in oral squamous cell carcinoma (SCC), these markers in AC could be used to indicate premalignancy in the lip. AC may be linked to altered expression of - catenin, a protein involved in cell adhesion and expression.

Hereditary disorders

There are a few known inherited disorders related with enhanced risk of malignancy in the oral cavity, such as Fanconi‟s anemia, Dyskeratosiscongenita, Epidermolysisbullosa, Xerodermapigmentosum and Bloom‟s syndrome.

Fanconi'sanaemia (FA)

The FA is difficult genetic syndrome which is relatedwithrisk of congenital malformations, bone marrow failure and cancer. It is a rare autosomal recessive syndrome caused by defects in approximately11genes involved in detection and repair of DNA.Those types of patients are characterized by aplastic anaemia with progressive bone marrow failure, congenital abnormalities, and a high tendency to malignancies including head and neck cancer. In the absence of alcohol and tobacco exposure, 14% of anaemic patients develop head and neck squamous cell carcinomas by the age of 40s.Orally, there is a manifestation of generalized black hyperpigmentation on the buccalmucosa, tongue and palate associated with severe generalized periodontitis reported in patients with Fanconi‟sanaemia. Traditional highlights of FA are short height, thumb or spiral beam anomalies, microcephaly, and proof of bone marrow brokenness. FA has been determined in grown-up patients to have not many or missing evident old style clinical highlights, and can likewise be the finding in seriously influenced babies with the VACTERL range of variations from the norm (vertebral inconsistencies, butt-centric atresia, heart deformities, tracheo-esophageal fistula with esophageal atresia, basic renal and appendage irregularities). The main clinical highlights of FA are hematological; FA is the commonest sort of acquired bone marrow disappointment disorder and the rates of aplastic frailty, myelodysplastic condition, and intense myeloid leukemia are for the most part significantly expanded in homozygotes. The influenced FA patient may give dying, paleness and repeating contaminations.

Dyskeratosiscongenita

Dyskeratosiscongenita (DC) is first portrayed by Zinsser in 1906 and was perceived as clinical substance by Cole (1930)&Engman (1926).DC patient's experience the ill effects of BMF that influences 80%–90% of cases by age 30 years and is the main source of death.The pulmonary fibrosis and malignant growth are serious intricacies during advancement of the sickness. It is an acquired BMF condition described by strange skin pigmentation, BMF, and malignant growth inclination, with expanded danger for squamous cell carcinoma and hematolymphoid neoplasms. DC is heterogeneous at hereditary level, contingent upon the influenced quality. DC might be acquired in X-connected, autosomal prevailing (AD), or autosomal latent (AR) designs.Oral leukoplakia has been reported in 80% of dyskeratosiscongenita patients and it may affect any mucosal surface, but the oral mucosa is most commonly affected with the tongue the most frequently affected site.

Xerodermapigmentosum

Xerodermapigmentosum is a rare neurocutaneous disease with a recessive mode of inheritance which may affect all races worldwide the lips are the most frequently affected and show epithelia atrophy, telangiectasia and hyperpigmentation and this may occasionally be seen in oral mucosa.Most cases of Xerodermapigmentosum start in early childhood and are fatal by 20 years age. There is an improvedoccurrenceofmalignanciescontaining oral cancer.

CONCLUSION

OPMDs have an expanded danger of forming into oral malignant growth. A few assortments are perceived. Some of them are singular injuries while others alluded to as conditions which are multifocal or boundless inside oral pit. Leukoplakia is very widely recognized oral PMD experienced in clinical practice. Generally harmful movement in these sores is just of the request for 5%. A limit of half of extreme dysplasias, 30% of moderate dysplasias and not many (5%) gentle dysplasia are thought to advance to disease.Therefore, early understanding of their clinical as well as histopathological aspects is very essential for timely intervention of oralcancer.

BIBLIOGRAPHY

1. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009; 45(4-5): 309-16.
2. Bachar G, Hod R, Goldstein DP, Irish JC, Gullane PJ, Brown D, Gilbert RW, Hadar T, Feinmesser R and Shpitzer T. Outcome of oral tongue squamous cell carcinoma in patients with and without known risk factors. Oral Oncol. 2011; 47(1):45-50.
3. Myers JN, Elkins T, Roberts D and Byers RM. Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes. Otolaryngol Head Neck Surg. 2000; 122(1):44-51.
4. Morse DE, PsoterWJ, Cuadrado L, Jean YA, Phelan J, Mittal K, Buxo CJ, Cruz GD and Elias A. A deficit in biopsying potentially premalignant oral lesions in Puerto Rico. Cancer Detect Prev. 2009; 32(5):424-30.
5. Van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral Oncol. 2009; 45(4-5):317-23.
6. Warnakulasuriya S, Johnson NW, Van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med 2007;36:575-80.
7. Napier SS and Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. J Oral Pathol Med. 2008; 37(1):1-10.
8. Van der Waal I and AxellT.Oral leukoplakia: a proposal for uniform reporting. Oral Oncol. 2002; 38(6):521-6.
9. Axell T, Pindborg JJ, Smith CJ and van der Waal. Oral white lesions with special reference to precancerous and tobacco- related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18-21 1994. International Collaborative Group on Oral White Lesions. J Oral Pathol Med. 1996; 25(2): 49-54.
10. Gupta PC, Mehta FS, Daftary DK, Pindborg JJ, Bhonsle RB, Jalnawalla PN, Sinor PN, Pitkar VK, Murti PR, Irani RR, Shah HT, Kadam PM, Iyer KS, Iyer HM, Hegde AK, Chandrashekar GK, Shiroff BC, Sahiar BE and Mehta MN. Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. Community Dent Oral Epidemiol. 1980; 8(6): 283-333.
11. Ishii J, Fujita K, Munemoto S and KomoriT. Management of oral leukoplakia by laser surgery: relation between recurrence and malignant transformation and clinicopathological features. J Clin Laser Med Surg. 2004; 22(1):27-33.
12. Jaber MA, Porter SR, Speight P, Eveson JW and Scully C. Oral epithelial dysplasia: clinical characteristics of western European residents. Oral Oncol. 2003; 39(6): 589-96.

13. Rajendran R. Oral leukoplakia (leukokeratosis): Compilation of facts and figures. J Oral MaxillofacPathol2004;8:58-68.
14. Waal IV. Oral leukoplakia; a proposal for simplification and consistency of the clinical classification and terminology. Med Oral Patol Oral Cir Bucal. 2019 Nov 1;24 (6):e799-803.
15. Schepman KP, Van der Waal I. A proposal for a classification and staging system for oral leukoplakia: a preliminary study. European Journal of Cancer Part B: Oral Oncology. 1995 Nov 1;31(6):396-8.
16. Richardson MS, Spruill L, Neville B. Proliferative VerrucousLeukoplakia:Review of an Evolving Entity. AJSP: Reviews & Reports. 2016 May 1;21(3):132-7.