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EVALUATION OF CASES OF EXOPHYTIC VERRUCOUS HYPERPLASIA IN ORAL SUBMUCOUS FIBROSIS IN BIHAR

Dr. Richa Dubey
MDS, Assistant Professor, Department of Dentistry, Netaji Subhash Medical College & Hospital, Bihta, Patna, Bihar, India.

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Corresponding author: Dr. Richa Dubey
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Abstract
Verrucous hyperplasia probably represents a morphological variant of verrucous carcinoma by Slootwage J P and Muller H (1983). An essential feature in distinguishing verrucous hyperplasia from verrucous carcinoma is the location of the thickened epithelium with respect to adjacent normal appearing epithelium. In verrucous hyperplasia most of the hyperplastic broadened rete ridges lay above the adjacent normal epithelium while verrucous carcinoma on contrary exhibits a downward growth pattern of otherwise similar rete ridges. Hence based on above findings the present study was planned in Evaluation of Cases of Exophytic Verrucous Hyperplasia in Oral Submucous Fibrosis in Bihar.
The present study was planned in Department of Dentistry, netaji subhash Medical College & Hospital, Bihta, Patna, Bihar. Conventional oral examination (COE) of 30 patients with Oral submucous fibrosis (OSMF) was performed using incandescent operatory light. Out of that 6 cases having Verrucopapillary lesion were evaluated in the present study.
The data generated from the present study concluded that patients with highly suspicious malignant verrucous growths on VEL scope examination exhibited increased auto fluorescence and on histopathological examination revealed no signs of dysplasia or invasion. Exhibition of increased autofluorescence of these lesions on VELscope examination could greatly help to determine their nondysplastic nature.
Keywords: Verrucous hyperplasia, Verrucous carcinoma, Oral Submucous Fibrosis, etc.

Introduction

In 1952, Schwartz coined the term atrophica idiopathica mucosa oris to describe an oral fibrosing disease he discovered in 5 Indian women from Kenya. [1] Joshi subsequently coined the termed oral submucous fibrosis (OSMF) for the condition in 1953. [2]

Oral submucous fibrosis is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). Oral submucous fibrosis results in marked rigidity and an eventual inability to open the mouth. [3, 4] The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx. [5]

The condition is well recognized for its malignant potential and is particularly associated with areca nut chewing, the main component of betel quid. [6] Betel quid chewing is a habit practiced predominately in Southeast Asia and India that dates back to thousands of years. It is similar to tobacco chewing in westernized societies. The mixture of this quid, or chew, is a combination of the areca nut (fruit of the Areca catechu palm tree, erroneously termed betel nut) and betel leaf (from the Piper betel, a pepper shrub), tobacco, slaked lime (calcium hydroxide), and catechu (extract of the Acacia catechu tree). [3] Lime acts to keep the active ingredient in its freebase or alkaline form, enabling it to enter the bloodstream via sublingual absorption. Arecoline, an alkaloid found in the areca nut, promotes salivation, stains saliva red, and is a stimulant.

The ingredients and nomenclature of betel quid vary by region as detailed below [7, 8] :

Pan: This is freshly prepared betel quid (with or without tobacco).

Gutka (gutkha, guttkha, or guthka): This is a manufactured version of betel quid with tobacco sold as a single-use sachet. It is primarily used on the Indian subcontinent (ie, India, Pakistan, Bangladesh). Betel quid without tobacco is mostly used in Southeast Asian countries (ie, Taiwan, Myanmar, Thailand, China, Papua New Guinea, Guam).

Pan masala: This is a commercially manufactured powdered version of betel quid without tobacco used in the Indian subcontinent.
Pan Parag: It is a brand name of pan masala and gutka used in India.
Mawa (kharra): This is a crude combination of areca, tobacco, and lime.

Mainpuri tobacco: Popular in parts of northern India, Mainpuri tobacco is a mixture of areca nut, tobacco, lime,

and various condiments. Depending on local preferences, sweeteners or spices (ie, cardamom, saffron, clove, anise seed, turmeric, mustard) are also added as flavorings.

In most patients with oral submucous fibrosis, areca nut was chewed alone more frequently than it was chewed in combination with pan (ie, betel leaf plus lime plus betel catechu, with or without tobacco) [4] or had a higher areca nut content. [9]

The pathogenesis of the disease is not well established, but the cause of oral submucous fibrosis is believed to be multifactorial. A number of factors trigger the disease process by causing a juxtaepithelial inflammatory reaction in the oral mucosa. Factors include areca nut chewing, ingestion of chillies, genetic and immunologic processes, nutritional deficiencies, and other factors.

The areca nut component of betel quid plays a major role in the pathogenesis of oral submucous fibrosis. In a 2004 study, a clear dose-dependent relationship was observed for both frequency and duration of chewing areca nut (without tobacco) in the development of oral submucous fibrosis. Smoking and alcohol consumption alone, habits common to areca nut chewers, have been found to have no effect in the development of oral submucous fibrosis, but their addition to areca nut chewing can be a risk for oral submucous fibrosis. Commercially freeze-dried products such as pan masala, guthka, and mawa have higher concentrations of areca nut per chew and appear to cause oral submucous fibrosis more rapidly than self-prepared conventional betel quid, which contains smaller amounts of areca nut. [9]

Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen by 150%. In one study, arecoline was found to elevate the mRNA and protein expression of cystatin C, a nonglycosylated basic protein consistently up-regulated in a variety of fibrotic diseases, in a dose-dependent manner in persons with oral submucous fibrosis. [10]

In 3 separate but similar studies, keratinocyte growth factor-1, insulinlike growth factor-1, and interleukin 6 expression, which have all been implicated in tissue fibrogenesis, were also significantly up-regulated in persons with oral submucous fibrosis due to areca quid chewing, and arecoline may be responsible for their enhanced expression. Further studies have shown that arecoline is an inhibitor of metalloproteinases (particularly metalloproteinase-2) and a stimulator of tissue inhibitor of metalloproteinases, thus decreasing the overall breakdown of tissue collagen.

Insertion/deletion 5A polymorphism in the promoter region of the matrix metalloproteinase-3 gene, which results in alteration of transcriptional activities, has also been found in persons with oral submucous fibrosis but not in those with oral squamous cell carcinoma. Conversely, insertion/deletion 2G polymorphism in the promoter of the matrix metalloproteinase-1 gene has been implicated in oral squamous cell carcinoma but not oral submucous fibrosis. [11]

Flavanoid, catechin, and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation. This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown. Oral submucous fibrosis remains active even after cessation of the chewing habit, suggesting that components of the areca nut initiate oral submucous fibrosis and then affect gene expression in the fibroblasts, which then produce greater amounts of normal collagen. Chewing areca quid may also activate NF-kappaB expression, thereby stimulating collagen fibroblasts and leading to further fibrosis in persons with oral submucous fibrosis. [12]

Areca nuts have also been shown to have a high copper content, and chewing areca nuts for 5-30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis that copper acts as an initiating factor in persons with oral submucous fibrosis by stimulating fibrogenesis through up-regulation of copper-dependent lysyl oxidase activity. Further, a significant gradual increase in serum copper levels from precancer to cancer patients has been documented, which may have a role in oral fibrosis to cancer pathogenesis.

The role of chilli ingestion in the pathogenesis of oral submucous fibrosis is controversial. The incidence of oral submucous fibrosis is lower in Mexico and South America than in India, despite the higher dietary intake of chillies. A hypersensitivity reaction to chillies is believed to contribute to oral submucous fibrosis. One study demonstrated that the capsaicin in chillies stimulates widespread palatal fibrosis in rats, while another study failed to duplicate these results. [13]

A genetic component is assumed to be involved in oral submucous fibrosis because of the existence of reported cases in people without a history of betel nut chewing or chilli ingestion. Patients with oral submucous fibrosis have been found to have an increased frequency of HLA-A10, HLA-B7, and HLA-DR3. [4]

An immunologic process is believed to play a role in the pathogenesis of oral submucous fibrosis. The increase in CD4 and cells with HLA-DR in oral submucous fibrosis tissues suggests that most lymphocytes are activated and that the number of Langerhans cells is increased. The presence of these immunocompetent cells and the high ratio of CD4 to CD8 in oral submucous fibrosis tissues suggest an ongoing cellular immune response that results

in an imbalance of immunoregulation and an alteration in local tissue architecture. These reactions may be the result either of direct stimulation from exogenous antigens, such as areca alkaloids, or of changes in tissue antigenicity that lead to an autoimmune response. [14]

Further, the major histocompatibility complex class I chain–related gene A (MICA) is expressed by keratinocytes and other epithelial cells and interacts with gamma/delta T cells localized in the submucosa. MICA has a triplet repeat (GCT) polymorphism in the transmembrane domain, resulting in 5 distinct allelic patterns. In particular, the phenotype frequency of allele A6 of MICA in subjects with oral submucous fibrosis is significantly higher and suggests a risk for oral submucous fibrosis. [15]

Some authors have demonstrated increased levels of proinflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) in patients with oral submucous fibrosis, which may be central to the pathogenesis of oral submucous fibrosis. [16]

Iron deficiency anemia, vitamin B complex deficiency, and malnutrition are promoting factors that derange the repair of the inflamed oral mucosa, leading to defective healing and resultant scarring. [4] The resulting atrophic oral mucosa is more susceptible to the effects of chilies and betel nuts.

Some authors have found a high frequency of mutations in the APC gene and low expression of the wild-type TP53 tumor suppressor gene product in patients with oral submucous fibrosis, providing some explanation for the increased risk of oral squamous cell carcinoma development in patients with oral submucous fibrosis. Other studies have suggested that altered expression of retinoic acid receptor-beta may be related to the disease pathogenesis. [17]

The term oral submucosal fibrosis derives from oral (meaning mouth), submucosal (meaning below the mucosa of the mouth), and fibrosis (meaning hardening and scarring). Chewable agents, primarily betel nuts (Areca catechu), contain substances that irritate the oral mucosa, making it lose its elasticity. Nutritional deficiencies, ingestion of chilies, and immunologic processes may also have a role in the development of oral submucous fibrosis. Oral submucous fibrosis is rare in the United States and is found only in the immigrant members of the South Asian population who chew betel nuts.

Worldwide, estimates of oral submucous fibrosis indicate that 2.5 million people are affected, with most cases concentrated on the Indian subcontinent, especially southern India. The rate varies from 0.2-2.3% in males and 1.2-4.57% in females in Indian communities. Oral submucous fibrosis is widely prevalent in all age groups and across all socioeconomic strata in India. A sharp increase in the incidence of oral submucous fibrosis was noted after pan parag came onto the market, and the incidence continues to increase. Oral submucous fibrosis also occurs in other parts of Asia and the Pacific Islands. Migration of endemic betel quid chewers has also made oral submucous fibrosis a public health issue in many parts of the world, including the United Kingdom, South Africa, and many Southeast Asian countries. [18]

Oral submucous fibrosis occurs on the Indian subcontinent, in Indian immigrants to other countries, and among Asians and Pacific Islanders as a result of the traditional use of betel quid endemic to these areas.

The male-to-female ratio of oral submucous fibrosis varies by region, but females tend to predominate. In a study from Durban, South Africa, a distinct female predominance was demonstrated, with a male-to-female ratio of 1:13. This was later confirmed by others, with a male-to-female ratio of 1:7. In addition, a female predominance in areca nut chewing was also noted in this region. Studies in Pakistan reported a male-to-female ratio of 1:2.3. [4]

Conversely, a case-control study of 185 subjects in Chennai, South India revealed a male-to-female ratio 9.9:1. In Patna, Bihar (also in India), the male-to-female ratio was 2.7:1. [19] With the onset of new commercial betel quid preparations, trends in sex predominance and age of occurrence may shift.

The age range of patients with oral submucous fibrosis is wide and regional; it is even prevalent among teenagers in India. In a study performed in Saipan, 8.8% of teenagers with a mean age of 16.3 years (± 1.5 y) were found to have oral submucous fibrosis. Generally, patient age ranges from 11-60 years; most patients are aged 45-54 years and chew betel nuts 5 times per day.

Oral submucous fibrosis has a high rate of morbidity because is causes a progressive inability to open the mouth, resulting in difficulty eating and consequent nutritional deficiencies. Oral submucous fibrosis also has a significant mortality rate because of it can transform into oral cancer, particularly squamous cell carcinoma, at a rate of 7.6%. [4]

No treatment is effective in patients with oral submucous fibrosis, and the condition is irreversible. Reports claim improvement of the condition if the habit is discontinued following diagnosis at an early stage. [20]

Patients with oral submucous fibrosis have an increased risk of developing oral cancer. The malignant potential and the origin of cancer are attributed to the generalized epithelial atrophy associated with oral submucous fibrosis. Tobacco is the component of the quid believed to be most associated with cancer development. However, the carcinogenic property of the areca nut was discovered

after noticing that cancer occurred in patients who chewed the nut without tobacco. In vitro, betel nut extracts increase the rate of cell division, reduce cell cycle time, induce DNA strand breaks, and induce unscheduled DNA synthesis. Whether the use of tobacco in addition to areca nuts is responsible for the increased risk of oral cancer is controversial because evidence is conflicting.

Verrucous hyperplasia probably represents a morphological variant of verrucous carcinoma by Slootwage J P and Muller H (1983). Essential features in distinguishing verrucous hyperplasia from verrucous carcinoma are the location of the thickened epithelium with respect to adjacent normal appearing epithelium. In verrucous hyperplasia most of the hyperplastic broadened rete ridges lay above the adjacent normal epithelium while verrucous carcinoma on contrary exhibits a downward growth pattern of otherwise similar rete ridges. Hence based on above findings the present study was planned in Evaluation of Cases of Exophytic Verrucous Hyperplasia in Oral Submucous Fibrosis in Bihar.

Methodology:

The present study was planned in Department of Dentistry, Netaji subhash Medical College & Hospital,bihta, Patna, Bihar. Conventional oral examination (COE) of 30 patients with Oral submucous fibrosis (OSMF) was performed using incandescent operatory light. Out of these 6 cases having Verrucopapillary lesion were evaluated in the present study.

All the OSMF cases were diagnosed on clinical grounds of restricted mouth opening and confirmed histologically.[1] Patients with exophytic verrucopapillary lesions (VPLs) mimicking malignancy in the background of OSMF were a part of the present study. Following COE, autofluorescence, examination of patients were conducted using VELscope (LED Medical Diagnostics Inc., Burnaby Canada). Photo documentation of all these VPLs was carried out during COE and VELscope examination for future comparison and analysis.

All the patients gave informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Results & Discussion:

Cancer is an important public health problem in many parts of the world. According to the International Agency for Research on Cancer of the World Health Organization (IARC– WHO), cancer rates are expected to increase at an alarming rate: from 10 million new cases globally in 2000 to 15 million in 2020. [21] Oral cancer is among the 10 most common cancers worldwide, and is especially seen in disadvantaged elderly males. Most cancers of the oral cavity are oral squamous cell carcinomas (OSCC), and tobacco, alcohol and betel use are the main risk factors. [22]

Verrucous hyperplasia probably represents a morphological variant of verrucous carcinoma by Slootwage J P and Muller H (1983). [23] Essential features in distinguishing verrucous hyperplasia from verrucous carcinoma is the location of the thickened epithelium with respect to adjacent normal appearing epithelium. In verrucous hyperplasia most of the hyperplastic broadened rete ridges lay above the adjacent normal epithelium while verrucous carcinoma on contrary exhibits a downward growth pattern of otherwise similar rete ridges.

Verrucous hyperplasia was described by Shear and Pindborg in 1980. It is more superficial and does not extend deeper than the surrounding normal epithelium. It shows dysplasia and can later develop into verrucous carcinoma or squamous cell carcinoma.

Oral verrucous carcinoma (VC) is a rare tumor first described by Lauren V. Ackermann in 1948. It is a special form of well-differentiated squamous cell carcinoma with specific clinical and histological features. Various names are used in the literature to describe this entity, including Ackerman's tumor, Buschke-Loewenstein tumor, florid oral papillomatosis, epithelioma cuniculatum, and carcinoma cuniculatum. The tumor grows slowly and locally, is invasive in nature and unlikely to metastasize. [24] It appears as a painless, thick white plaque resembling a cauliflower. The most common sites of oral mucosal involvement include the buccal mucosa, followed by the mandibular alveolar crest, gingiva, and tongue. Shear and Pindborg described a condition termed verrucous hyperplasia (VH) in 1980. Both lesions closely resemble each other clinically and pathologically. VH has been considered an antecedent stage or early form of VC and is believed to have the same biological potential. While histopathology is the gold standard in diagnosis, it is a subjective assessment of tissue, with inter- and intra-rater variability. [25] Surgery has been the first choice of treatment for these lesions, and radiotherapy is controversial; however, surgery combined with radiotherapy is the next most preferable treatment and may have benefits, particularly in cases of extensive lesions. If left untreated for years, a focus within VC may progress to invasive squamous carcinoma and release metastases. Recurrence rate is high in cases in which either irradiation or surgery alone is performed. [26]

Table 1: Basic Details

Parameters	No. of Cases
Age	23 – 35 years
Inter-incisal opening (mm)	20 – 35 mm
Size of the lesion (cm)	1 – 2 cm

Table 2: Clinicopathological features

Case	Site of VPL	VELscope appearance	Histopathological diagnosis
1	Right buccal gingiva	Fluorescence visualization loss	Oral verrucous carcinoma
2	Right commissure extending onto right buccal mucosa	Combination of Fluorescence visualization increase & Loss	Oral verrucous carcinoma
3	Left lateral border of tongue	Fluorescence visualization loss	Oral squamous cell carcinoma
4	Right buccal mucosa	Fluorescence visualization increase	Exophytic verrucous hyperplasia without dysplasia
5	Maxillary right labial mucosa	Fluorescence visualization increase	Exophytic verrucous hyperplasia without dysplasia
6	Right buccal mucosa	Fluorescence visualization increase	Exophytic verrucous hyperplasia without dysplasia

Table 3: Histopathological features of verrucopapillary lesions

Histopathological features	Observed in No. of Cases
Keratinized verrucopapillary processes	6
Keratin plugs	6
Epithelial lining: Parakeratinized	6
Epithelial hyperplasia:	
Basal cell hyperplasia	6
Acanthosis	6

OSMF is a precancerous condition associated with chronic betel nut chewing. The development of squamous cell carcinoma is seen in one-third of the OSMF patients, but the development of verrucous carcinoma is rare in such patients.

Chang et al., [28] in their study, suggested that chewing areca quid is the major risk factor in the development of verrucous hyperplasia and verrucous carcinoma.

A distinction should be made between verrucous hyperplasia and verrucous carcinoma. Verrucous hyperplasia was described by Shear and Pindborg in 1980. [27] It is more superficial and does not extend deeper than the surrounding normal epithelium. It shows dysplasia and can later develop into verrucous carcinoma or squamous cell carcinoma.

Verrucous carcinoma, on the other hand, extends more deeply, pulling the adjacent normal epithelium at its margin. It is diagnosed by histopathologic examination following excisional biopsy. Bulut et al., [29] in their study on 12 cases of oral verrucous carcinoma, showed that it is difficult to distinguish verrucous hyperplasia and verrucous carcinoma clinically. Verrucous hyperplasia is an antecedent or early form of verrucous carcinoma and should be treated as verrucous carcinoma and a close follow-up should be made.

Histopathologically blunt variety predominates sharp variety as opposed to sharp variety reported by Shear M and Pindborg JJ (1980). [30] This difference may be attributed to lesser sample size in present study. Hyperorthokeratinization was predominant in sharp variety and parakeratinization was predominant in blunt variety. Increase in thickness of stratum spinosum is responsible for verrucous type morphology of lesion. As proposed by Shear and Pindborg considerable acanthosis with broadened rete ridges causes deprivation of distant epithelial cells from blood supply and becomes edematous and swollen. These necrotic cells undergo desquamation, leaving cleft in the surface of the epithelium. Verrucous projections are formed in this way in between clefts. This also explains the presence of the papillary projections of laminapropria, which support the verrucous projections. At a later stage both the verrucous projections and the clefts between them undergo keratinization.

Histologically, verrucous hyperplasia shows three patterns: verrucous (most common), flat, and papillary (least common).13 It is characterized by the presence of parakeratinized epithelium showing papillary or verrucous growth with thin rete ridges and connective tissue papillae extending up to the surface. The papillae characteristically consists of foam cells also called xanthoma cells (xanthos = yellow).These xanthoma cells contain lipid as well as periodic acid Schiff (PAS) positive, diastase-resistant granules. There is a controversy over the exact origin of xanthoma cells but they are said to be a descent of monocytes/macrophages. However, there is no evidence of dysplasia. Macrophages are responsible for the initiation of process. As the epithelium degenerates due to local trauma, there is accumulation of epithelial breakdown products which induce inflammatory response and subsequent release of lipid material through the epithelium that finally is scavenged by the macrophages. They also suggested a local irritant as the initiator of the process. [31] Nowparast et al suggested that foam cells may be responsible for verrucous and papillary architecture which affects the nutrition and metabolism of the epithelial cells, leading to the hyperkeratotic change. [32]

Conclusion:

The data generated from the present study concluded that patients with highly suspicious malignant verrucous growths on VELscope examination exhibited increased autofluorescence and on histopathological examination revealed no signs of dysplasia or invasion. Exhibition of increased autofluorescence of these lesions on VELscope examination could greatly help to determine their nondysplastic nature.

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