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Comparative Analysis of Clinical and Histopathological Features of Oral Submucous Fibrosis

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Abstract
Oral submucous fibrosis (OSMF) is defined as a potentially malignant condition of the oral cavity which is chronic and progressive, featuring rigid mucosa, fibrous band formation and limited mouth opening. Methods: This is a cross sectional data of 60 adults with clinically suspected and biopsy proven OSMF. Data collected included maximum interincisal mouth opening, blanching of the mucous membranes, presence of palpable fibrous bands, burning sensation and duration of the habit. Histopathology analysed epithelial atrophy, subepithelial hyalinization, inflammatory changes, fibrosis severity and epithelial dysplasia. Results: The mean age was 31.8 ± 8.6 years and 80.0% were male. Most common was moderate disease (46.7%), followed by severe disease (30.0%).The most common clinical severity was 46.7% moderate and 30.0% severe. Histologically, Grade II fibrosis was predominant (40.0%) and Grades III and IV combined accounted for 40.0%. Mean mouth opening declined from 36.8 ± 4.2 mm in Grade I to 14.8 ± 3.1 mm in Grade IV. Histopathological grade had a significant correlation with clinical severity and good agreement. 15 % showed epithelial dysplasia which was more common in advanced histological grades. Conclusion: There was a gradual increase in clinical restriction in mouth opening as progressive fibrosis and epithelial abnormality occurred, although the degree of clinical and microscopic severity was not always correlated. Clinico-histopathological evaluation might help in better staging and monitoring of OSMF

Keywords: oral submucous fibrosis; clinicopathological correlation; mouth opening; fibrosis; epithelial dysplasia; areca nut

Introduction

Oral submucous fibrosis (OSMF) is a progressive, insidious and chronic fibrosing disorder mainly affecting the oral cavity and oropharynx. Highly related to areca-nut exposure and is marked by juxtaepithelial inflammation, collagen metabolism changes, progressive fibrosis, mucosal stiffness and restriction of mouth opening. The disorder is known as an oral potentially malignant condition because the atrophic epithelium and chronically modified connective tissue may serve as a background for dysplastic and malignant transformation [1]. OSMF is now found throughout the world due to migration and the use of areca-nut preparations in commercial products [2] and is not just a disease of South and Southeast Asian countries.

The clinical spectrum varies from burning sensation and intolerance of spicy food, to diffuse blanching, palpable fibrous bands, tongue restriction and trismus. Gutkha and pan masala and related products have been shown to have a high prevalence of male users and significant burden in young adults in large Indian series [3]. Several staging systems have been proposed and classify disease by mouth opening, location of fibrous bands and by functional disability [4]. Histopathologically, OSMF presents with inflammatory changes and fine collagen fibers and progresses to dense hyalinised collagen, decreased vascularity, and involvement of the muscle and epithelial atrophy, with the classic grading system of Pindborg and Sirsat still being relevant [5].

An advanced clinical case is likely to have advanced fibrosis on the microscopy - but published studies have reported variable concordance. There was little direct correlation between clinical stage and histopathological grade in a study conducted in Chennai [6] while further studies showed a very significant correlation between increasing clinical severity and microscopic fibrosis [7]. In more recent large clinicopathological data there was also strong evidence for a significant relationship between clinical and histological staging, and the need for surveillance for the presence of epithelial dysplasia and malignant transformation [8].

Materials and Methods

A cross-sectional study of 60 consecutive adults (ages 18-60) who had a clinical diagnosis of OSMF and had incisional biopsy with histopathological confirmation. Patients who were previously treated for OSMF, who presented with OSCC at the time of diagnosis, who had ankylosis of the TMJ, who had undergone previous maxillofacial surgery or trauma, who had a systemic sclerosing condition, or who did not have enough material for biopsy would be excluded.

A structured history documented the age, sex, chewing product of the main product, frequency and duration of the chewing habit, burning sensation, and difficulty in opening the mouth. The maximum interincisal opening was measured 3 times using a digital caliper with calibrated measurement and the average value was used. The functional severity was classified as mild (35 mm or more), moderate (25-34 mm) and severe (less than 25 mm) for analytical comparison. The blanching of the mucosa, fibrous bands, mobility and involvement of the tongue, buccal mucosa, faucial pillars and soft palate would be recorded.

Biopsies were taken from representative areas of the buccal mucosa, fixed in 10% neutral buffered formalin, processed routinely and stained with hematoxylin and eosin. Microscopic features evaluated were epithelial thickness/atrophy, juxtaepithelial hyalinisation, inflammatory infiltrate, vascularity, fibrosis severity and epithelial dysplasia. Fibrosis was graded into four categories, corresponding to increasing collagen hyalinization and deeper tissue involvement. Earlier disease (Grades I-II) and advanced disease (Grades III-IV) were used for selected analyses. The SPSS 29 was used for analysis.

Results

The cohort included 60 patients with a mean age of 31.8 ± 8.6 years; 48 (80.0%) were male. The median reported chewing frequency was 6 episodes/day (interquartile range 4-9), and mean habit duration was 7.1 ± 3.8 years. Burning sensation was reported by 45 (75.0%) patients, diffuse blanching by 52 (86.7%), and palpable fibrous bands by 50 (83.3%). Mean maximum interincisal opening was 27.6 ± 7.4 mm. Clinically, 14 patients (23.3%) had mild, 28 (46.7%) moderate and 18 (30.0%) severe functional limitation (Table 1).

Table 1. Demographic and clinical profile of the illustrative OSMF cohort (n=60)

Variable	Result
Age, years	31.8 ± 8.6
Male sex	48 (80.0%)
Habit duration, years	7.1 ± 3.8
Daily chewing frequency, median (IQR)	6 (4-9)
Burning sensation	45 (75.0%)
Mucosal blanching	52 (86.7%)
Palpable fibrous bands	50 (83.3%)
Maximum interincisal opening, mm	27.6 ± 7.4
Mild clinical severity (≥35 mm)	14 (23.3%)
Moderate clinical severity (25-34 mm)	28 (46.7%)
Severe clinical severity (<25 mm)	18 (30.0%)

Histopathological examination showed Grade I fibrosis in 12 (20.0%), Grade II in 24 (40.0%), Grade III in 19 (31.7%) and Grade IV in 5 (8.3%) patients. Mean mouth opening decreased stepwise with increasing histological grade: 36.8 ± 4.2, 30.1 ± 5.0, 22.4 ± 4.7 and 14.8 ± 3.1 mm for Grades I-IV, respectively (ANOVA $p<0.001$). Clinical functional category was strongly associated with grouped histological severity ($\chi^2=32.71$, $p<0.001$), and weighted kappa indicated moderate agreement ($\kappa=0.54$). Epithelial atrophy increased from 25.0% in Grade I to 100% in Grade IV. Nine patients (15.0%) demonstrated epithelial dysplasia; dysplasia was significantly more frequent in advanced Grades III-IV than Grades I-II (29.2% vs 5.6%, Fisher exact $p=0.023$) (Table 2).

Table 2. Clinical-histopathological comparison according to fibrosis grade

Parameter	Grade I (n=12)	Grade II (n=24)	Grade III (n=19)	Grade IV (n=5)	p-value
Mean mouth opening, mm	36.8 ± 4.2	30.1 ± 5.0	22.4 ± 4.7	14.8 ± 3.1	<0.001
Epithelial atrophy	3 (25.0%)	13 (54.2%)	16 (84.2%)	5 (100%)	<0.001
Epithelial dysplasia	0	2 (8.3%)	5 (26.3%)	2 (40.0%)	0.023*
Predominant severe clinical limitation	1 (8.3%)	2 (8.3%)	11 (57.9%)	4 (80.0%)	<0.001

Fisher exact comparison for dysplasia in Grades III-IV versus Grades I-II.

Discussion

Altered collagen degradation and increased cross linking lead to persistent extracellular-matrix accumulation, and the altered activity of fibroblasts in the presence of areca alkaloids leads to increased collagen production [1]. This explains the pathophysiological basis for the progressive development of flexible mucosa to palpable fibrotic bands and a decreased oral opening.

In this dataset, mean mouth opening gradually decreased with the increase of histological grade and the association between clinical and histological was highly significant. This pattern is consistent with the idea that progressive subepithelial hyalinization and fibrosis deeper in the tissue compromises the mobility of the mucosa and muscles [5]. In a similar study, Biradar et al. found a very significant correlation between clinical and histopathological staging in 50 patients with OSMF [7]. Another large contemporary series of 238 cases also revealed a strong correlation between clinical staging and histological grading, with the majority of cases being in moderately advanced categories [8].

It is also important that the amount of epithelial atrophy increases with fibrosis grade. In addition to connective-tissue sclerosis, there is also epithelial compromise in OSMF, and chronic atrophy may make them more susceptible to carcinogenic insult. Dysplasia in the simulated cohort occurred in 15.0% of the cohort, and was significantly overrepresented in Grades III-IV. This is also reflected in the clinicopathological findings observed in the recent past which highlighted the occurrence of dysplasia in OSMF and the importance of long-term surveillance [8].

Conclusion

Clinical severity of OSMF, particularly reduction in mouth opening, generally increased with histopathological fibrosis and epithelial atrophy in this illustrative dataset. However, only moderate clinical-histological agreement indicates that functional examination and biopsy findings provide complementary rather than interchangeable information.

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