# A CORRELATIVE STUDY OF HISTOLOGICAL STAGING AND CLINICAL SEVERITY OF TRISMUS IN PATIENTS WITH ORAL SUBMUCOUS FIBROSIS

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**ABSTRACT**

**BACKGROUND**

Oral submucous fibrosis (OSF) is a potentially malignant disease that primarily affects any part of the oral cavity and sometimes the pharynx. The disease is chronic, insidious and progressive in nature. It causes mucosal rigidity resulting in discomfort, burning and limitation of opening of the mouth. Blanching of the oral mucosa is an important clinical feature seen in the early stage of OSF. The present study had been undertaken to correlate the clinical staging of mouth opening with histopathological grading in OSMF patients. We wanted to morphometrically quantify the histopathological changes in oral submucous fibrosis and to correlate them with grading and clinical severity of trismus.

**METHODS**

78 patients diagnosed clinically were subjected to biopsy of the lesions from their periphery and compared with the normal areas. The criteria proposed by Pindborg and Sirsat (1966), who described four consecutive stages based upon sections stained with haematoxylin and eosin were used. The stages were classified as: 1) Very early stage: Characterized by fine collagen dispersed with marked oedema, prominent fibroelastic response dilated and congested blood vessels and inflammatory cells (mainly polymorphs and eosinophils). 2) Early stage: Early hyalinization in juxta epithelial area with thickened separate bundles of collagen and clumps of young fibroblasts in moderate number. 3) Moderately advanced stage: Moderately hyalinized collagen, the amorphous change starting from the juxta-epithelial basement membrane.

**RESULTS**

Among 78 patients with OSF, 57 were males (73.07%) and 21 were females (26.92%). Among them, histologically 19 (24.35%) were of very early stage, 27 (34.61%) of early stage and 22 (28.20%) of moderately advanced stage and 10 (12.82%) patients were in advanced stage. Collagenization was observed in 17/22 of moderately severe OSF and 10/10 of severely affected OSF. The thickness of the epithelium and subepithelial collagen showed no statistically significant differences between the different stages. However, blood vessel density was indirectly proportional to the histological stages. Histological stages directly correlated the frequency of trismus, but the severity of trismus showed no relation to the epithelial thickness or collagenization.

**CONCLUSIONS**

The thickness of the epithelium and subepithelial collagen should not be included in the histological staging criteria of oral submucous fibrosis. Probably the degree of hyalinization of collagen fibres and involvement of muscle fibres are more important in causing trismus, rather than a simple increase in the subepithelial collagen thickness.

**KEYWORDS**

Oral Submucous Fibrosis, Trismus, Spices, Histological Staging and Morphometry.

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## BACKGROUND

Oral sub mucous fibrosis (OSF) is a tropical disease commonly encountered in Indian and South East Asia.[1] OSF is a disease with insidious onset and tends to be chronic affecting any part of the oral cavity and sometimes the pharynx and oesophagus.[2] Its characteristic feature is loss of mucosal supple resulting in mucosal rigidity of varying intensity. This is due to the fibroelastic changes taking place in the juxta epithelial layer of mucosa. Gradual deposition of fibrous tissue leads to a progressive inability to open the mouth (Trismus). Various etiological agents were suggested

to be playing a role in its causation either individually or collectively. They are spices, nutritional deficiency, chewing of areca nut, genetic susceptibility, altered salivary constituents, and autoimmunity and collagen disorders.[3] OSF is a well-recognized, potentially premalignant condition. Malignant transformation rates as high as 7.6% have been reported from the Indian subcontinent over a 17 year period.[4] The alkaloid, arecoline released from the areca nut appears to increase the deposition of collagen, the major extracellular matrix molecule in the subepithelial zone.[5,6] This accumulation increases with the severity of the disease.[7,8] Animal experiment studies and in vitro culture studies of human fibroblast proved to analyse the aetiopathogenesis of OSF in addition to simple case reports, population-based studies or hospital-based case control studies over the past several decades by dental researchers and oral pathologists reported different aspects of OSF.[9] In spite of Histopathological studies with light microscopy and transmission and scanning electron microscopy[10] yet, there is paucity of studies, which correlate the clinical features to the various histopathological changes of OSF. The present study biopsied the lesions from clinically diagnosed (palpable bands on the buccal mucosa) OSF and analysed morphometrically and findings were correlated with the histological staging as well as with the clinical severity of trismus- to rationalize whether those pathological changes have any practical implication in disease progression and also to find out any relation between the clinical severity of OSF and its histological stages.

## METHODS

After obtaining Institutional committee ethical clearance this study was conducted with an ethical committee cleared consent form. This study was conducted in the department of ENT, Mediciti Institute of Medical Sciences and Hospital, Medchal, Hyderabad- 501401 over a period of 2 years from March 2016 to February 2018.

### Inclusion Criteria

1) Patients aged between 17 to 57 years were included. 2) Patients with suspicion of having OSF (palpable white bands in the buccal cavity) were included. 3) Patients with history of using Pan, Gutka and spices in excess were included.

### Exclusion Criteria

1) Patients with benign ulcerative conditions of the oral cavity or pharynx were excluded. 2) Patients with recent history of surgery of the oral cavity or Oropharynx were excluded. 3) Patients with history of injury to temporomandibular joint were excluded. All the patients were biopsied by the concerned surgeon from the periphery of the lesion to compare it with the normal areas. Tissues were for histopathological examination. Biopsy bits with adequate presence of epithelial layer, subepithelial zone including the muscle layer were considered for further evaluation. Histological staging of OSF was done. The reporting pathologist was same for all the patients and the criteria proposed by Pindborg and Sirsat (1966),[11] who described four consecutive stages based upon sections stained with Haematoxylin and eosin were used.

The stages were classified as: 1) Very early stage: Characterized by fine collagen dispersed with marked oedema, prominent fibroelastic response dilated and congested blood vessels and inflammatory cells (mainly polymorphs and eosinophils). 2) Early stage: Early hyalinization in juxta epithelial area with thickened separate bundles of collagen and clumps of young fibroblasts in moderate number. 3) Moderately advanced stage: Moderately Hyalinized collagen, the amorphous change starting from the juxta-epithelial basement membrane. Occasionally thickened collagen bundles are seen separated by slightly residual oedema. The fibroblast response is less marked. Blood vessels are either normal or constricted as, a result of increased surrounding fibrous tissue. Inflammatory exudates consist of lymphocytes, plasma cells and occasional eosinophils. 4) Advanced stage: Collagen becomes completely Hyalinized and seen as smooth sheets with no separate bundles discernible. Oedema was absent. Hyalinized areas are devoid of fibroblasts, although their elongated cells or vestigial nuclei were seen at rare intervals along the fibre bundles. Blood vessels are completely obliterated or narrowed. Lymphocytes and plasma cells are variably present. Clinicopathological correlation was done with histological staging of OSF and clinical staging of trismus. Finally, the clinical staging of trismus was correlated retrograde with the histological staging. Pearson's chi square test was applied for that purpose and values less than 0.05 were considered statistically significant.

## RESULTS

78 patients with OSF were included in this study. There were 57 males (73.07%) and 21 females (26.92%), (Table 1). Out of 78 patients with OSF, histologically 19 (24.35%) were of very early stage, 27 (34.61%) of early stage and 22 (28.20%) of moderately advanced stage and 10 (12.82%) patients were in advanced stage. Gender wise distribution of incidence of OSF was tabulated in Table 1.

| Gender | Very Early Stage 19 | Early Stage 27 | Moderately Advanced Stage 22 | Advanced Stage 10 |
|---|---|---|---|---|
| Male- 57 | 12 (15.38%) | 22 (28.20%) | 18 (23.07%) | 09 (11.53%) |
| Female- 21 | 07 (08.97%) | 05 (06.41%) | 04 (05.12%) | 01 (01.28%) |

***Table 1. Showing the Gender Incidence and Incidence of Staging of OSF (n-78)***

All the cases of advanced stage had atrophied epithelium. Very early stage cases did not show any measurable amount of collagenization. Between the different stages of OSF the collagen thickness showed no statistically significant differences ($F = 0.85$, $p > 0.05$). Early stage cases showed no significant differences from the Very early stage, but moderately advanced stage and Advanced stage showed a highly significant statistical difference from the same. The number of blood vessels is directly

proportional to the vessel reaction, which may be either due to an increased number of endothelial cells or blood vessel density. White bands were seen on the buccal mucosa, OSF involving the gingivolabial sulcus with tobacco stained teeth, and in patients with OSF (advanced stage), and the inter-incisional distance was measured in each patient using a slide callipers scale. When trismus was correlated with the histological staging and morphometric findings, it was found that the frequency of trismus was directly proportional to the histological stages of OSF; advanced the histological stages, more the number of patients having trismus. However, the severity of trismus showed relation neither with the histological staging nor with the degree of collagenization (Table 2).

| Observations | Very Early Stage 19 | Early Stage 27 | Moderately Advanced Stage 22 | Advanced Stage 10 |
|---|---|---|---|---|
| Thickness of epithelium | Normal | Normal | < 0.2 mm | < 0.1 mm |
| Collagenization | Absent | Absent | 17/22 | 10/10 |
| Collagen thickness | Negligible | Negligible | 0.6 mm | 0.9 mm |
| White bands (number) | Absent | Absent | 14 | 18 |
| Blood vessel density | Normal | Normal | Less than 0.6 mm | Less than 0.3 mm |
| Inter-incisional teeth distance (mean values) | Normal | Normal | 1.36±0.85 cms | 0.74±0.45 cms |

***Table 2. Showing Histopathological Observations Compared to Trismus (n-78)***

## DISCUSSION

OSF is a crippling disease of the oral mucosa, as in its later stages due to trismus. Patients are unable to chew and consume food leading to malnutrition. It is a premalignant condition, which is seen in Indians and Southeast Asians, with overall prevalence rate in India to be about (0.2–0.5%). Gender distribution of OSF shows wide variation in the literature. Few epidemiological surveys in India have shown a male predominance. However, female predominance in the occurrence of this entity had also been shown in few studies. Males were affected in the present study could be due to easy accessibility for males to use areca nut and its products more frequently than females in our society, whereas females being more conscious about their aesthetic, health, and moral values, and moreover, the study was conducted in a rural area. Hence, the lifestyle is different than the urban areas. In the present study 25 patients were in the age range of 17–27 years, with a mean age of 21.45±2.10 years. 31 patients were in the age group of 28 to 37 years with a mean age of 31.20±4.80 years. 11 patients were in the age group of 38 to 47 years with a mean age of 43.75±2.65 years. 11 patients were in the age group of 48 to 57 years with a mean age of 49.05±1.35 years. Hence, it can be concluded that the occurrence of OSF is seen most commonly in younger age group of 17 to 37 years. These findings coincided with the studies of Kiran Kumar et al,[12] Pandya et al,[13] Hazarey et al, [14] Shivakumar[15] Goel et al,[16] and Angadi.[17] The observation of our study was different from that of Pindborg and Sirsat,[11] who reported the maximum number of OSF cases were in the age group of 40-49 years in their study. This changing trend of the disease presently indicates the involvement of more number of younger age group and this could be because of increased social encounters and economic liberty they get at this age in a rapidly developing nation like India. Therefore, during this age, they indulge in various chewing habits such as betel nut, Gutka, paan masala, smoking, alcohol, etc., either to relieve stress, as a fashion or due to peer pressure.

In this study it was observed that in patients with OSF the overlying epithelium may have varying thickness regardless of the stages of OSF. However, advanced stage disease is commonly associated with atrophy that may be due to chronicity of the disease. Pindborg and Sirsat (1966),[11] also suggested that the overlying epithelium is either atrophic or hyperplastic, often hyperkeratotic. Again the progression of the disease was not found to be related to the degree of collagenization. In another two different studies that the severity of trismus did not correlate with the different stages of OSF.[12,18] Therefore, the statement that trismus occurs due to increase in subepithelial collagen deposition is an oversimplification as was concluded by some authors in some studies.[8,9] Probably hyalinization of the collagen fibres (in which they become stiff) rather than the simple increase in collagen thickness and involvement of muscle fibres (collagen fibres in-between muscle bundles) along with the site of involvement appear to be more important in causing trismus. Pindborg and Sirsat[11] described the very early stages by the presence of fine fibrillar collagen dispersed with marked edema with increasing thickness in higher stages of disease.[11] Huang IY, Shieh TY[7] also found that accumulation of collagen fibres increases with the severity of the disease. In the initial stages there is an increase in the number of blood vessels along with dilatation and congestion-early stage showing highest dilatation. That may be due to compensatory or reactive to the environmental insults in the form of alkaloid (from areca nut), chronic irritation or infection etc. At the later advanced stages probably these mechanisms become decompensated due to persistent insults resulting in constriction or obliteration of the blood vessels along with a decrease in their number. These findings are similar to the study results of Fang CY et al.[19] who showed the increase in micro vessel quantity and quantity density in the early stages and the decrease in micro vessel quantity, quantity density, micro vessel area and area density in the middle and the late stages. They concluded that the presence of micro vessel hyperplasia occurred in the early stages of oral submucous fibrosis. Similarly, Pindborg and Sirsat[11] suggested dilatation and congestion of blood vessels in the early stages and constriction to obliteration at the later stages.

## CONCLUSIONS

The thickness of the epithelium and subepithelial collagen should not be included in the histological staging criteria of

oral submucous fibrosis. Probably the degree of hyalinization of collagen fibres and involvement of muscle fibres are more important in causing trismus, rather than a simple increase in the subepithelial collagen thickness.

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