Opinion

Histopathology of Oral Submucous Fibrosis in Third Dimension with an Additional note on Hypothesis of Epithelial Atrophy

Sandhya Tamgadge, Avinash Tamgadge

Department of Oral and Maxillofacial Pathology and Microbiology, D. Y. Patil Deemed to be University, School of Dentistry, Nerul, Navi Mumbai, Maharashtra, India

Abstract

Oral submucous fibrosis (OSMF) is a potentially malignant disorder, characterized by progressive fibrosis of the lamina propria and underlying connective tissue. It has high chances of malignant transformation. It is caused by betel nut which is very common habit among Indians. Thus, regular monitoring of histopathological changes is mandatory by physicians, private practitioners, and oral pathologists. Therefore, histopathological changes should be understood by everyone who is into health care. This article is a preliminary report on three-dimensional (3D) images and 3D-animation video of histopathological aspect of OSMF designed by author herself, for better understanding of histopathological aspect, which has never been reported so far. Additional hypothesis on epithelial atrophy have also been proposed.

Keywords: Animation, epithelial atrophy, histopathology three-dimensional, hypothesis, images, oral submucous fibrosis, video

Introduction

Oral submucous fibrosis (OSMF) is a chronic, debilitating disease, characterized by the inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). It results in marked rigidity and an eventual inability to open the mouth. The condition is well recognized for its malignant potential and is particularly associated with areca nut chewing.[1] The pathogenesis of OSMF is not well established and hence is believed to be multifactorial. The cascade begins with a juxta-epithelial inflammatory reaction in the oral mucosa, interspersed with healing and fibrosis, with trismus being the end result. It is generally agreed that the pathological alteration in OSMF begins in the lamina propria, and the epithelium responds only secondarily to it.[2]

Researchers have been trying to find out a complete cure. Hence, it is crucial to know the histopathological process by everyone whoever deals with such patients. Therefore, preliminary three-dimensional (3D) images and 3D-animation video of histopathological aspect of OSMF have been designed to make all researchers, students, and practitioners to understand the basic etiopathogenesis, as such work have not been reported so far [Video 1].

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Histopathology

Subepithelial changes

It shows two major changes: (1) fibrosis of the lamina propria and (2) muscle changes [Flowchart 1].

Fibrosis of the lamina propria

As per literature, the pathomechanisms underlying the development of fibrosis have been partially elucidated[3] [Figures 1-3].

The role of inflammation in the development of OSMF is similar to the healing response. Therefore, the inhibition of the inflammatory response in injured tissues is considered as a promising strategy to limit the development of fibrosis.[4]

The barrier function of superficial layers of the oral epithelium has been confirmed by experiments that demonstrate an

Address for correspondence: Dr. Sandhya Tamgadge, Department of Oral and Maxillofacial Pathology and Microbiology, D. Y. Patil Deemed to be University, School of Dentistry, Nerul, Navi Mumbai - 400 706, Maharashtra, India.
E-mail: sandhya.tamgadge@gmail.com

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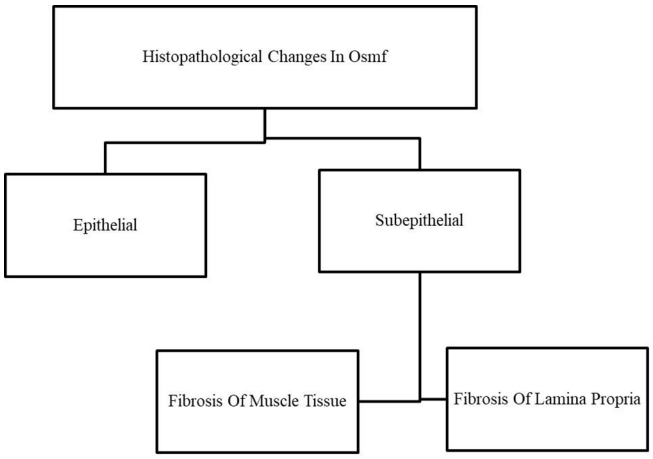

Flowchart 1: Histopathological changes in oral submucous fibrosis

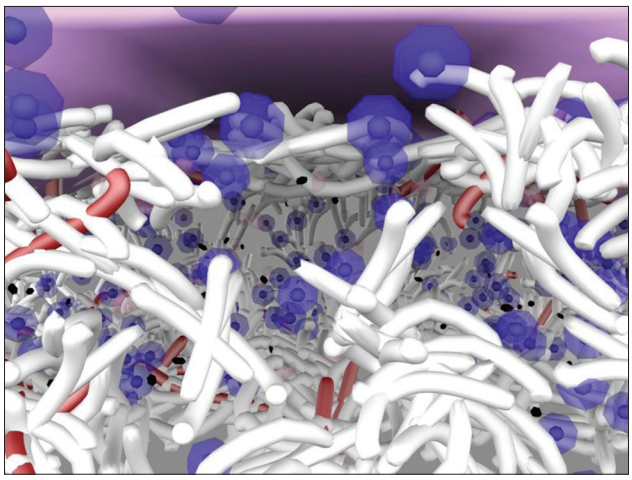

Figure 2: Three-dimensional image shows dense accumulation of collagen fibers and inflammatory cells

increase in permeability when the surface layers are removed by stripping leads to the formation of major pathways for large molecules, across stratified epithelium, through the intercellular spaces.[4]

Meyer *et al*. also highlighted the strong association between barrier function impairment, inflammation, and dermal fibrosis.[5] Similarly, in OSMF, microtrauma resulting from continuous areca nut chewing leads to loss of integrity of the epithelium which allows the penetration of toxic molecules through intercellular spaces into the connective tissue (CT) stroma and evokes an inflammatory response. This further results in fibrosis as a part of the healing phenomenon. Defective intercellular junctions lead to fibrosis as a part of healing process has also been mentioned by Krieg *et al*.[6]

Muscle changes

N. G. EI.-Ladhan mentioned that in OSMF, the degenerative process not only involves the muscle fibers but also its surrounding connective tissue. This was characterized by scanty collagen fibrils and the accumulation of edematous-like fluid around these muscles. If this is the case, then restricted

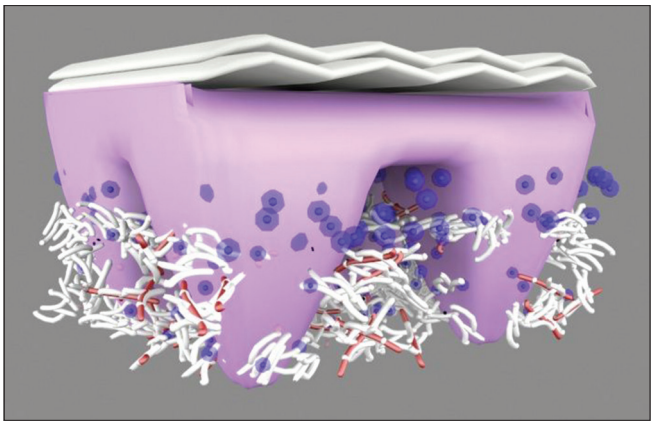

Figure 1: Three-dimensional image shows fibrosis of subepithelial tissue

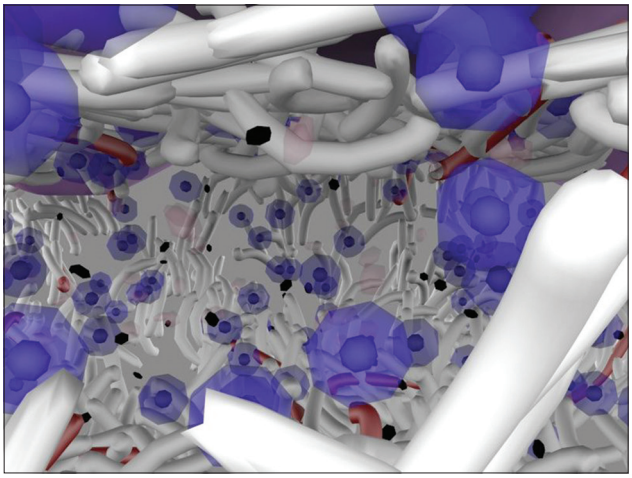

Figure 3: Three-dimensional image shows inner view of stroma

mouth opening would appear to depend not only on subepithelial fibrosis but also on the extent of muscle damage, due to edema and fibrosis.[3,7-9]

Trismus in OSMF may be related to loss of a variety of extracellular matrix (ECM) molecules including elastin and replacement of muscle fibers by homogeneous collagen Type I.[9]

Epithelial changes

Figures 4 and 5 shows normal epithelium and atrophic epithelium in third dimension.

The basic etiology for epithelial atrophy has been suggested by many researchers is still not clear and still considered as assumptions and hypothesis.[3]

Various explanations have been proposed by various researchers, as follows:

1. It is the aftermath of heavy fibrosis in the underlying connective tissue.
2. It is a result of malnutrition.
3. Few hold the view that the epithelium has become stretched.
4. It is thinned by the changes in the underlying connective tissue.

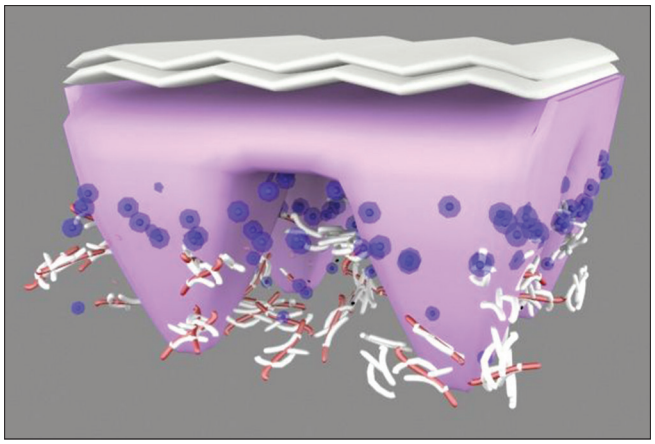

Figure 4: Three-dimensional image shows normal epithelium, keratin on the surface, and collagen fibers and blood vessels with white blood cells in the stroma

Epithelial hyperplasia could be an adaptive response to local irritants to provide a greater degree of protection to the underlying tissues. The hyperplastic epithelial response and later atrophy probably reduce the barrier function of the mucosa to local irritants.[10]

There could be one more hypothesis based on four research evidences collectively, as follows:

First evidence – Effect of masticatory forces on the width of the oral epithelium

It is suggested that the length of rete ridges is positively correlated with the strength of mechanical stresses on the mucosa.[11,12] Hence, masticatory mucosa usually has longer rete ridge than lining mucosa, as amount of physical forces are directly proportional to the length of rete ridges.

Wu *et al*. stated that rete pegs are well developed in dentulous patients as compared to edentulous, as seen in old age, where the muscle forces are decreased, and less force is transmitted to rete pegs which leads to atrophy of the epithelium.[11,12]

Second evidence – Effect of stroma on overlying epithelium

Recent studies also showed that stromal cells and their matrices can influence the upper epidermis development; therefore, oral epithelium too structurally depends on underlying lamina propria.[11]

Third evidence – Lamina densa, anchoring fibrils, and lamina propria, a unit

In the oral mucosa, some juxta epithelial collagen fibrils of the lamina propria curved toward the epithelial cells and passed through the anchoring fibril network and apparently merged with the basal surface of the lamina densa. Thus, Adachi and Hayashi stated that there is a direct connection of juxta epithelial collagen fibrils with lamina densa which could be a ubiquitous anchoring system to stabilize the epithelial tissues.[13]

Adachi *et al*. also proposed that collagen V might also be involved in anchoring of epithelia to underlying connective tissues.[14] Thus, tension in underlying connective tissue will have a direct effect on rete pegs through the lamina densa.

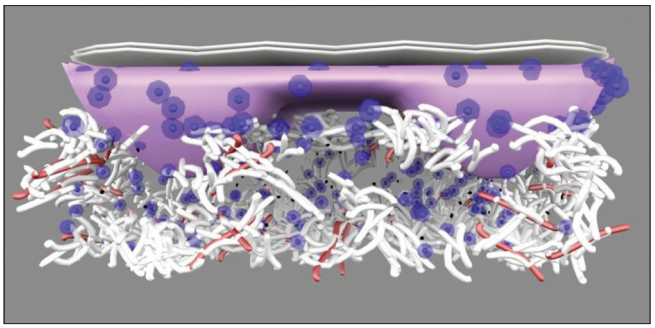

Figure 5: Three-dimensional image shows histopathology of oral submucous fibrosis showing epithelial atrophy with dense fibrosis

Fourth evidence – Facial muscle force is directly transmitted to the oral epithelium

The potential of force transmission between skeletal muscles through inter- and extra-muscular connective tissues has been demonstrated. Investigators have definitively shown that epimuscular pathways can transmit substantial force. Thus, it could also be hypothesized that orofacial muscle forces are transmitted to adjacent CT stroma and reach directly to the oral epithelium through anchoring fibrils, as cheek and lip muscles do not have bony insertions.[15] Thus, when muscle undergoes complete fibrosis, in OSMF, the muscle force does not reach the oral epithelium due to fibrous connective tissue present in between muscles and overlying epithelium, leads to disuse atrophy.

Nevertheless, this hypothesis cannot be applied to fibrosis of the hard palate as it does not have muscles but still undergoes fibrosis. Here, the epithelial atrophy could be related to microtrauma due to continuous chewing of the areca nut which leads to inflammation and fibrosis similar to the healing process as suggested by Huub Maas *et al*.[15]

Cheek and lip muscles do not have bony insertions and tendons; therefore, the force of contraction will get transmitted to the oral epithelium through the connective tissue and anchoring fibrils, as all these tissues are connected as unit as mentioned earlier. Chi Zhang stated that two pathways are involved in transmitting force from muscle fibers to tendon: (1) longitudinal transmission, i.e., transmission along the muscle fibers through the myotendinous junctions to the tendon and (2) lateral transmission, i.e., transmission laterally across one muscle fiber to the adjacent connective tissue network, the ECM, and finally to the tendon.[16] However, cheek and lip muscles do not have bony insertions; therefore, the force gets transmitted to the surrounding connective tissue.[16]

Conclusion

Thus, it can be finally be hypothesized that when severe fibrosis takes places in the lamina propria and underlying muscles, the muscle functions are limited. Therefore, the contractile force

does not reach the epithelium through the fibrosed lamina propria and anchoring fibrils. Due to which rete pegs do not get stretched by muscle pull and epithelium undergo disuse atrophy.

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Conflicts of interest

There are no conflicts of interest.

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