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RESEARCH ARTICLE
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"SUBMUCOSAL FIBROSIS AS A BARRIER TO TUMOR EXTENSION: ANATOMICAL AND HISTOLOGICAL INTERPRETATION"

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ABSTRACT

Background: Oral submucous fibrosis (OSF) is a precancerous disorder that is associated with extensive submucosal collagen accretion. Its possible use as a hindrance to the spread of lymphatic tumors in oral squamous cell carcinoma is under-researched.

Objective: To determine submucosal fibrosis as an anatomical and histologic barrier to lymphatic metastasis and extranodal spread of oral squamous cell carcinoma at its advanced stage.

Materials and Methods: It was a 5-year prospective observational study involving 80 oral squamous cell carcinoma patients at stage III-IV, where the buccal mucosa, alveolus, or retromolar trigone showed the bony involvement. There were 50 patients with concomitant submucosal fibrosis (mostly at stage 3) and 30 without. Each of them was resected at the primary level with the modified radical neck dissection (levels I-V). The histopathologic parameters included nodal yield, metastatic involvement, and extranodal extension.

Results: Patients who had submucosal fibrosis had small nodal metastases (only to levels I-II in 40% and none in 60%), and no extranodal extension. Conversely, the extensive multi-level nodal disease (10 -17 positive nodes) in all patients without fibrosis was common, and the extranodal spread was common.

Conclusion: Submucosal fibrosis is a protective barrier that limits lymphatic dissemination and extranodal progression, which may improve the prognosis of OSF-related advanced oral cancers.

Keywords: *Oral submucous fibrosis, oral squamous cell carcinoma, lymphatic metastasis, extranodal extension, tumor barrier, neck dissection.*

INTRODUCTION

OSF is a potentially malignant, progressive, chronic disease, predominantly in the oral mucosa, in which fibrosis and overproduction of collagen in the submucosal tissues, otherwise related to the habit of chewing areca nuts, is excessive (1). The OSF pathogenesis is complicated and results in irreversible remodelling of tissues and malignancy (2). One of the major processes in this mechanism is the deposition of collagen that stiffens the tissue and changes the tumor microenvironment (3). The recent research has given special attention to the part played by epigenetic modification in the progressive fibrotic alteration in OSF (4). In addition, epistatic locus interaction has been attributed to persistence and progression of myofibroblast activity in this condition (5). In the gastrointestinal oncology literature, endoscopic submucosal dissection procedures can be applied to learn that submucosal layer can be a natural protection against the deeper tumor invasion (6). Similar preventive hydrogel applications with barrier properties have been applied after submucosal esophageal dissection to reduce stenosis (7).

The problem of mechanical rigidity caused by submucosal fibrosis is also one of the critical issues in the process of dental implantation in OSF patients with limited mouth opening (8). Another instance of the submucosa in restricting the spread of lesions and facilitating harmless resection is the state-of-the-art colorectal endoscopic submucosal dissection (9). Fibrotic tissue and its duality in tumor behavior are increasingly being seen by interventional gastroenterology in oncology (10). The epithelial-to-mesenchymal transition is one of the features of fibrotic disorders that disintegrate the integrity of the epithelial barrier in inflammatory bowel disease (11). The contribution of senescent epithelial cells in OSF in microenvironmental remodeling is that they secrete TGF-b1 which causes the constant deposition of collagen (12). This could also be applied to their use as such agents as epigallocatechin-3-gallate have been shown to inhibit the collagen accretion caused by arecoline and could have therapeutic implications (13). Another approach to gynecologic cancer fibrotic barriers is the creation of engineered nanoparticles with the potential to cross into dense collagen networks (14). Research studies are also progressing further on the pathogenesis of OSF, paying attention to how the condition develops out of the first injury to irreversible fibrosis (15). There is also an emerging evidence that chewing areca nuts could cause changes to the microbial dysbiosis, which result in altering the oral microbiome and submucous fibrosis development (16). The contacts between the tumor and fibrosis are bi-directional signaling that can lead to the rapid progression or cause physical obstacles to diffusion (17). Long-term nasopharyngeal and otic histopathological observations give information on the structural and immunopathological alterations that overlap with submucosal structural alteration in the OSF in chronic cases (18). It has been noted that submucosal fibrosis, which co-exists with it, is particularly at stage 3 and is correlated with a marked reduction in lymphatic metastasis, using clinical observations in patients with advanced oral squamous cell carcinoma.

A 5 year longitudinal study, which analyzed 80 patients, observed that 60 percent of the patients with submucosal fibrosis had no nodal extension and where nodal involvement was experienced, it was limited after modified radical neck resection. On the contrary, the 30 patients who never developed fibrosis experienced extensive lymphatic proliferation despite comparable tumor staging suggesting that these patients did not have positive prognosis due to aggressive metastatic progression. This rather protective action of submucosal fibrosis against its premalignant character is the reverse of the long-established premalignant character. It prevents access of tumor cells to the lymphatic vessels through the thick collagen netting which is an-atmospheric and histologically creates a stiff barrier that restricts extra-tumoral invasion. Such findings are in line with reported barriers to submucosal dissection and epithelial-mesenchymal interactions in fibrotic dissimilarity.

Objective: To measure the use of submucosal fibrosis as an anatomical and histological barrier to lymphatic tumor dynamics and extranodal dissemination in patients presenting with advanced oral squamous cell carcinoma.

MATERIALS AND METHODS

Study Design: prospective observational comparative study.
Study Settings: A tertiary care hospital specializing in head and neck oncology.
Duration of Study: The study spanned 5 years, from January 2020 to December 2024.
Inclusion Criteria: Patients with advanced oral squamous cell carcinoma (clinical stages III and IV) in the buccal mucosa, alveolus, or retromolar trigone with bony involvement (mandible or maxilla) were included. All the chosen patients needed the primary operation of neck dissection and modified radical testis. Cases that had clinically or histologically proven submucosal fibrosis (to the majority of stage 3) or none at all were enrolled to enable comparison of lymphatic spread patterns.
Exclusion Criteria: Patients with early oral cancer (I-II) who received non-surgical treatment (radiotherapy or chemotherapy) as the primary treatment, recurrent tumors, and distant metastases at the time of presentation were excluded. Those whose necks were not completely dissected, whose histology was not well documented, or had other underlying conditions that substantially affected the lymphatic drainage (had undergone surgery or radiation of the neck before) were also excluded to obtain an accurate measurement of nodal involvement in relation to submucosal fibrosis.

Methods

Advanced oral squamous cell carcinoma (stage III-IV) patients who had buccal mucosa, alveolus, or retromolar trigone with bony involvement (mandible or maxilla) were evaluated thoroughly in terms of trismus and palpable lymph nodes, and contrast-enhanced CT neck to evaluate nodal status. All the patients were scheduled to undergo primary surgical resection of the tumor with either segmental mandibulectomy or maxillectomy as needed, together with unilateral or bilateral modified radical neck dissection (levels I-V). Intraoperative clinical findings of submucosal fibrosis included tissue stiffness, and its presence was confirmed histologically in resected specimens. Greater than 70 percent of cases had stage 3 submucosal fibrosis. Specimens of neck dissection that were resected were carefully dissected, and the number of lymph nodes was counted and subjected to histopathological analysis to ascertain metastatic invasion and extranodal extension. Patients with and without submucosal fibrosis were compared with respect to nodal yield, positivity, and extranodal spread.

Results

A total of 80 patients with advanced oral squamous cell carcinoma (stages III-IV) were included in this 5-year observational study, comprising 50 patients with concomitant submucosal fibrosis (predominantly clinical and histological stage 3) and 30 patients without submucosal fibrosis. All patients had tumors involving the buccal mucosa, alveolus, or retromolar trigone with bony involvement (mandible or maxilla). More than 70% of cases were clinical stage III, while approximately 30% were stage IV. Preoperatively, palpable lymph nodes were detected in 10 patients with submucosal fibrosis, and CT scans suggested suspicious nodes in 12 additional patients in this group. All patients underwent primary tumor resection with modified radical neck dissection (levels I-V). Histopathological examination of neck dissection specimens revealed marked differences in lymphatic metastasis between the two groups.

Table 1: Preoperative Nodal Status Comparison

Parameter	With Submucosal Fibrosis (n=50)	Without Submucosal Fibrosis (n=30)
Palpable lymph nodes	10 (20%)	Not specified
CT-positive lymph nodes	12 (24%)	Not specified

In the submucosal fibrosis group, more than 70 lymph nodes were recovered from 20 patients, but only 2–3 nodes were positive for malignancy, confined to levels I and II. In the remaining 30 patients

with submucosal fibrosis, more than 70 lymph nodes were recovered, but none contained metastatic deposits. Notably, no extranodal extension was observed in any patient with submucosal fibrosis.

Table 2: Histopathological Nodal Yield and Positivity

Parameter	With Submucosal Fibrosis (n=50)	Without Submucosal Fibrosis (n=30)
Patients with >70 nodes recovered	50 (100%)	Not applicable
Positive nodes (total patients)	20 patients (2–3 nodes each, levels I-II)	30 patients (≥10–17 nodes each)
Patients with no positive nodes	30 (60%)	0 (0%)
Extranodal extension	0 (0%)	Present in multiple cases

In contrast, all 30 patients without submucosal fibrosis demonstrated extensive lymphatic spread. Despite similar or lower clinical staging in some cases, these patients had 10–17 positive lymph nodes per neck dissection specimen, with involvement across multiple levels and frequent extranodal extension.

The most striking finding was the complete absence of extranodal spread in the submucosal fibrosis cohort, despite advanced primary tumors with bone involvement. This suggests that the dense fibrotic submucosa acted as a mechanical and anatomical barrier, restricting tumor cell migration into lymphatic channels and preventing extranodal invasion.

Graph Description (Bar Graph): Comparison of Positive Lymph Nodes

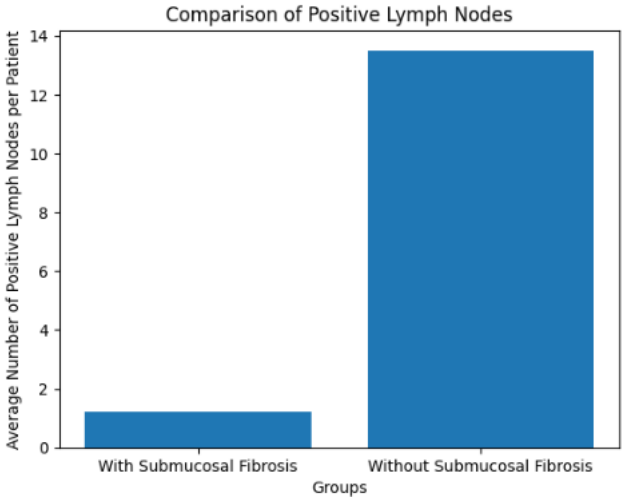

Table 3: Summary of Lymphatic Spread and Prognosis Indicators

Feature	With Submucosal Fibrosis (n=50)	Without Submucosal Fibrosis (n=30)
Lymphatic metastasis	Limited (40% low-volume)	Extensive (100% high-volume)
Levels involved	I–II only	Multiple levels
Extranodal extension	Absent	Present
Implied prognostic impact	Favorable (restricted spread)	Unfavorable (aggressive spread)

The implications of these findings are that submucosal fibrosis, which is a precancerous pathological entity itself, ironically plays a protective role in aggressive lymphatic spread and extranodal spread in advanced oral squamous cell carcinoma. The thick collagenous submucosal layer seems to make invasion by the tumors into the lymphatic vessels physically difficult, which translates to much reduced nodal burden and improved confinement of the disease to the primary site.

Discussion

Oral submucous fibrosis (OSF) is an insidious disease that is chronic and usually triggered by deposits of submucosal collagen and is primarily provoked by areca nut alkaloids and epithelial-mesenchymal transition (1). Recent comprehensive reviews have also identified new frontiers of avenues of OSF pathogenesis, including long-term signalling of myofibroblasts and extracellular matrix remodelling (2). Interestingly, however, as a consequence of excessive collagen accumulation, although loss of tissue softness can play out differently on the behaviour of tumours, the situation depend on the anatomy (3). Genes and environment interaction and epigenetic changes are also the factors that play a role in the persistence of fibrotic phenotype in OSF patients (4). It has been established that epigenetics-epistasis interaction is a significant trigger during the progression of the potentially malignant disease (5).

The concept of submucosal layer as a mechanical barrier is upheld in the literature of endoscopic submucosal dissection wherein the submucosa usually resists further invasions or progression of complications following the endoscopic submucosal dissection procedure (6). Likewise, the modulation of the submucosa of the esophagus is supposed to be done by potentiation of fibrotic response and stenosis of preventive measures of hydrogels following esophageal ESD (7). Other clinical dilemmas in dental implant placement among OSF patients with trismus are just an indication of the extreme 19937. The existence of highly complex endoscopic treatment of colon lesions is also used to understand how intact submucosal planes might help to restrict the spread of the tumor and offer an en blocresection (9). Oncology interventional approaches are becoming more conscious of the scenario in which there is a complex condition between fibrosis and tumor development in various sites (10).

Epithelial barrier dysfunction and mesenchymal transition is the main role played by fibrotic diseases, which is observed in intestinal fibrosis in cases of inflammatory bowel disease (11). The senescent epithelial cells in OSF release TGF-B1, which can increase collagen deposition and microenvironmental remodelling, which subsequently sustains fibrosis (12). The use of natural compounds such as epigallocatechin-3-gallate has shown a possibility of reducing arecoline-induced collagen deposition and this has offered potential therapeutic opportunities (13). Gynecologic cancers using the nanoparticle-based methods of dense collagen scaffolds emphasize the possibility of fibrotic barriers control to promote drug delivery (14). The progress of the knowledge about OSF since its clinical manifestation to the molecular processes is still being documented in the historical and the current reviews (15). New interacting and interrelating between microbial dysbiosis caused by Aspergillus or yeast, and new submucous fibrosis are realised.

This is a bi-directional tumor-stroma interaction in which fibrosis may be an induction of invasion through signaling by stiffness and an opposite inhibition of mechanically containing (17). The histopathological evidence of structural remodelling and immune dysregulation is observed in chronic nasopharyngeal disorders and these have been associated with submucosal modifications in OSF (18). The present paper provides clinical evidence of the protective role of submucosal fibrosis against lymphatic metastasis in already developed oral squamous cell carcinoma. Of 80 patients in a group, the 50 patients with the preponderance of the stage 3 submucosal fibrosis demonstrated a very less nodal involvement as compared to 30 patients with none. Despite a bony invasion of primary tumor, fibrosis group had small quantities of low volume metastasis at level I and II without extranodal spread. This is opposed to the non-fibrosis group wherein there was extensive multi-level nodal illness and extranodal dissemination which exists even in certain cases with comparatively lesser clinical staging.

The interpretation of these results is that a dense layer of hyalinized collagen in the OSF submucosa is a physical barrier that prevents access of tumor cells to lymphatic channels, which is synonymous to localizing tumor. The tumor is in direct contact with this rigid fibrotic layer, which may be the potential cause of the limited lymphatic metastasis, because of the anatomical location of the oral cancers of the patients of the OSF - typically buccal mucosa and alveolus. Stage 3 fibrosis is histologically characterised by collagen bands instead of normal submucosal structure that form a mechanical barrier against tumour dissemination beyond the primary site. Even though the fact that OSF is clearly defined as a premalignant condition that has excessive risk of malignant change demonstrates a high rate of malignant change, the research study exhibits a paradox of achievement in already developed carcinomas. The same fibrotic process that is predisposing to malignancy appears to provide protection against aggressive metastatic behavior in cancer that has taken place. This dichotomy is congruent with less specific generalizations in tumor-fibrosis interactions, in which thick desmoplastic reactions may limit propagation under particular conditions.

Particularly, it is of interest that the fibrosis cohort did not have extranodal extension, which is a strong adverse prognostic factor, and is associated with an increment in recurrence and poor prognosis. The locoregional and overall outcome of such patients can be improved through the prevention of extension and intrusion of periosteal tissues by submuscular fibrosis. Such are noteworthy clinical implications. Patients with oral cancer with OSF might possess a distinct biological population necessitating definite management methods. In some few cases the lower lymphatic metastasis rate would be given as a rationale to be more conservative in treating the neck but this would also have to be further proved. The balance between antifibrotic and profibrotic can also be applied in order to guide new treatment options to prevent the advancement of OSF or apply its shielding effect when treating the disease.

As it has been identified in this paper, submucosal fibrosis despite a premalignant potential is an excellent anatomical and histological defense against the growth and extranodal dissemination of lymphatic tumors in advanced oral squamous cell carcinoma. The dense submucosa, the collagenous, prevents the spreading of the metastasis, which gives the much more positive outcomes in terms of the disease containment and, perhaps, a better prognosis as compared to non-fibrotic ones.

Conclusion

This cross-sectional cohort of 80 patients with progressive oral squamous cell carcinoma proves that simultaneous submucosal fibrosis, largely at stage 3, is like a serious anatomical and histological safeguard against tumour lymphatic development and extranodal distribution. The metastatic nodal disease in the 50 patients with submucosal fibrosis was scanty and was limited to the level I-II with no extranodal spread, although the primary tumours were advanced with bony invasion. On the other hand, non-fibrotic patients (30) had widespread multi-level nodal metastasis and frequent extranodal spread, which is a characteristic of aggressive lymphatic spread and a more unfavourable prognosis. The thick collagenous submucosal layer is seemingly observed to provide physical hindrance to tumor access of the lymphatic channels, essentially localizing the disease. Even though oral submucous fibrosis is a premalignant lesion with its inherent risks, its prevalence in oral cancer itself supports the heterogeneous effect on metastatic behavior in the primary tumor. These results indicate a clear biological subgroup of OSF-related oral cancers that can be treated with specific prognostic evaluation and treatment approaches.

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