

The Stromal Dictators in a Concomitant Case of Oral Submucous Fibrosis - Oral Squamous Cell Carcinoma

Abstract

Oral submucous fibrosis (OSMF) is a potentially malignant disorder, characterized by alteration in the connective tissue stroma. Its association with oral squamous cell carcinoma (OSCC) has been recognized and conferred a special status as a distinct disease entity with improved prognosis as compared to conventional squamous cell carcinoma. Such cases of concomitant presentation of OSMF and OSCC have not yet been defined, leading to ambiguity regarding the evaluation. The concomitant occurrence of OSMF-OSCC is associated with histopathological features, unlike OSMF, yet similar to an aggressive presentation of OSCC. An indepth evaluation of the connective tissue, along with other tumor characteristics such as tissue hypoxia, inflammatory cell population, neoangiogenesis, and stromal cells fortify the possibility of these cases of concomitance being as aggressive, if not more, as compared to conventional OSCC. Thus, recognizing such cases along with the evaluation of probable prognostic indicators is necessary to improve the current understanding of tumorigenesis and progression in concomitant cases of OSMF-OSCC.

Keywords: Aggressiveness, concomitant oral submucous fibrosis and oral squamous cell carcinoma, tumor microenvironment

Introduction

India continues to bear about one-third of the global burden of oral cancer, with an incidence of nearly 1 lakh cases each year. Oral squamous cell carcinoma (OSCC) is often preceded by oral potentially malignant disorders (OPMDs).

Oral submucous fibrosis (OSMF) is one such OPMD which is highly prevalent in South-east Asia and is characterized by the changes in collagen fibers.^[1] Paymaster first reported the possible precancerous nature of OSMF.^[2] Variable figures derived from studies on the Indian population have reported the malignant transformation rate of OSMF between 4.5%–7.6%,^[3,4] and more recently as 0.2%–1.2%^[5] with a globally accepted rate of 7%–13%.^[6]

The authors have reported the cases of OSCC along with OSMF as early as 1968.^[4] An entity such as concomitant OSMF-OSCC has also been reported with a prevalence of 25.77%.^[1] Due to the lack of a clear definition of “concomitance” in this scenario, we propose to define it as cases that present, at a point in time, with

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the clinical features of OSMF along with a lesion that is histopathologically proven as OSCC.^[1] These cases of concomitant OSMF-OSCC have been reported in younger males demonstrating a better grade of OSCC differentiation with lesser nodal metastasis.^[7] Ray *et al.*^[5] and Chaturvedi *et al.*^[7] have regarded such cases as a distinct clinicopathological entity owing to its proposed areca-associated pathogenesis,^[8] hypothesized extracellular matrix alterations,^[8,9] and an overall better prognosis.

Case Report

A 47-year-old male presented with a swelling on the right side of the face along with a history of burning sensation for 1 month. The patient was a betel quid and tobacco habitué for the past 25 years.

On examination, the labial and buccal mucosa showed pallor, blanching along with bilateral and circumoral bands. The right buccal mucosa showed the presence of an ulceroproliferative lesion, measuring 3 cm × 2 cm. It had an indurated base was tender and bled on touch. Examination of regional lymph nodes revealed a single submental node and matted right

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submandibular nodes, both measuring 1.5 cm. They were fixed and tender. Contrast computed tomography of the neck revealed enlargement of level IB, level II, and prehyoid nodes.

Incisional biopsy reported a moderately differentiated squamous cell carcinoma. The stroma demonstrated minimal fibrosis, absence of hyalinization along with numerous budding capillaries, and moderate-to-dense chronic inflammatory cell infiltrate [Figure 1]. Perineural and perivascular invasion was noted. The above histopathological findings of OSCC when viewed in the context of clinically existent OSMF raise a query regarding the epithelial and stromal alterations that probably impact the prognosis and management. Thus, an analysis of the associated stromal alterations was undertaken to better understand the unique tumor microenvironment in cases of concomitance.

Using Masson's trichrome (histochemistry) for the assessment of early and mature collagen, minimal fibrosis, and absence of areas of hyalinization was confirmed [Figure 1]. Immunohistochemistry for the key microenvironmental features such as the presence of myofibroblasts, protumoral macrophages, extent of neoangiogenesis, and tissue hypoxia was investigated [Figure 2]. The stroma showed minimal positivity for α -smooth muscle actin (α -SMA) with most areas being obscured by dense inflammation. A 2+ distribution of CD-163(+) cells was noted, particularly around tumor islands, demonstrating diffuse infiltration of M-2 protumoral macrophages. CD-105, a marker specific for neoangiogenesis, highlighted the presence of numerous budding capillaries at the invasive front in the intervening stroma. Diffuse positivity for hypoxia-inducible factor (HIF- α) was noted throughout the epithelium and tumor islands. The evaluated stromal features are suggestive of an aggressive phenotype, creating a dilemma for prognostication.

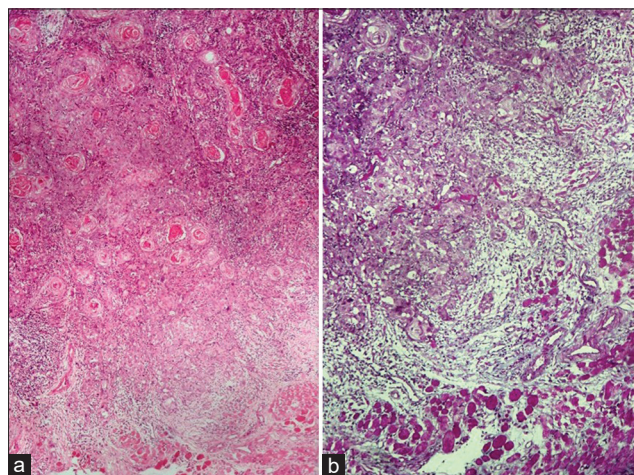


Figure 1: (a) Section of invasive front (H and E, x100) (b) Masson's trichrome

Discussion

OSMF predominantly and progressively involves the connective tissue compartment of the oral mucosa.^[3] Cases showing the progressive development of an epithelial pathology such as OSCC justify the categorization of OSMF as an OPMD.

The present case is in concurrence with the data reported by Bhola *et al.*^[10] who compared concomitant cases of OSMF-OSCC with the cases of OSCC only and examined the possibility of a better prognosis of the former. Much has been stated regarding the prognostic factors for OSCC, whereas prognostic indicators for OSCC concomitant with OSMF are yet to be explored. Limited data are available regarding the stromal modifications and behavior of concomitant cases.

We focused on four primary and relevant aspects of the tumor stroma in the scenario of concomitance. It has been hypothesized that fibrosis, as noted in OSMF, leads to claudication of blood vessels, resulting in a decrease in perfusion to the tissues. This has been regarded as a rate limiting step for tumorigenesis and spread, thus improved prognosis.^[5] While the exact mechanism has not been elicited, a similar effect of fibrosis on the lymphatic system lowers the incidence of nodal involvement.^[5]

Siriwardena *et al.*^[11] have reported no association between the degree of fibrosis and malignant transformation or the former and tumor differentiation. Alka *et al.*^[9] noted no significant variation in the expression of SMA between the cases of concomitance and OSCC alone. The minimal amount of fibrosis and the absence of hyalinization as in the current case is an intriguing finding when viewed in the context of OSMF and OSCC. The same is corroborated by the minimal positivity for SMA and demands inquiry into the underlying stromal process that leads to such contrasting findings.

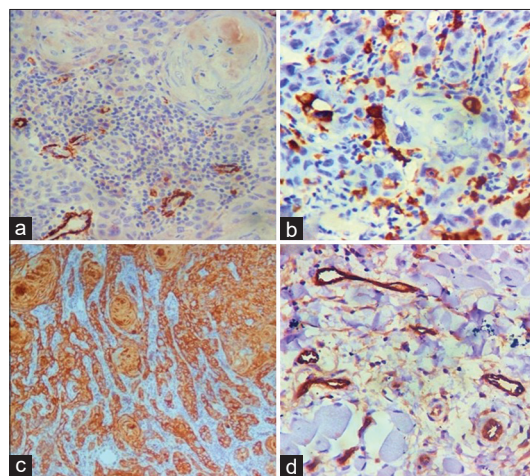


Figure 2: (a) Minimal positivity for smooth muscle actin ($\times 400$) (b) Positivity for CD-163 (TAM's) ($\times 400$) (c) HIF- α positive epithelium and tumor islands ($\times 100$) (d) CD-105 positive blood vessels ($\times 400$)

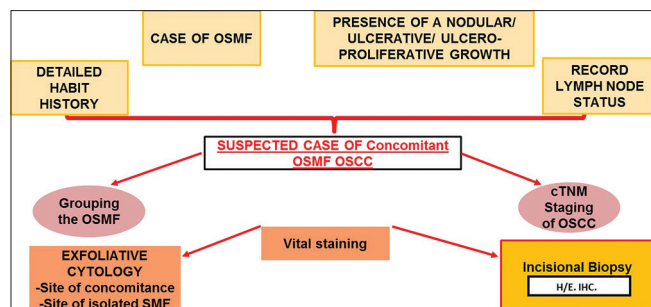


Figure 3: A diagnostic work up for concomitant cases of oral submucous fibrosis oral squamous cell carcinoma must include clinical staging and histopathological evaluation of the epithelial and stromal alterations that drive tumorigenesis and progression

The diffuse positivity for HIF- α in this case is in agreement with the increase in hypoxia as reported by Chaudhary *et al.*^[12] CD-105-positive vessels are suggestive of a metabolic shift and an attempt of the stroma to cope with the increase in demand for tissue perfusion. No previous data regarding the inflammatory component in such cases of OSMF-OSCC exist a protumoral infiltrate of M2 macrophages was noted. The aggressive nature of the lesion in this particular case is fortified by the extensive involvement of lymph nodes and the rapid progression of the disease.

While it may be premature to attribute a better prognosis to concomitant cases, further investigation regarding the clinical course of the disease along with the tumor microenvironment is warranted [Figure 3]. As illustrated through this case, in the concurrent scenario of OSMF-OSCC, alterations in the tumor stroma may actually potentiate the aggressiveness of the tumor and alter expected behavior.

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Conflicts of interest

There are no conflicts of interest.

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