Mini-Review

T cell subset—an overview in oral submucous fibrosis and oral squamous cell carcinoma in background of oral submucous fibrosis

Roopa Yadahalli^, Gargi S. Sarode, Sachin C. Sarode

Department of Oral Pathology and Microbiology, Dr. D. Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pimpri, India

Contributions: (I) Conception and design: GS Sarode, R Yadahalli; (II) Administrative support: SC Sarode; (III) Provision of study materials or patients: GS Sarode, R Yadahalli; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: SC Sarode; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Roopa Yadahalli, MDS. Department of Oral Pathology and Microbiology, Dr. D. Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Sant Tukaram Nagar, Pimpri, Pune 411018, India. Email: roopa.madalli@gmail.com.

Abstract: Oral submucous fibrosis (OSF) is a precancerous condition with marked alteration in fibers of connective tissue concerned with the lamina propria and its deeper position. In the period of about 10 years the OSF has shown 7.6% of the malignant transformation (MT) rate. The immune system is also known to play the utmost significant part in the regulation of OSF and frank invasive lesions. The passable host immune response defends the mucosa from its malignant change of it. With the progress of time, it is getting very apparent that counts and functionality of various T cell subset in different diseases and links between T cells profile and pathological symptoms or the predisposition for the disorders is becoming important. Recent studies concerning the immune system have discovered about the host immune could affect tumor growth, accenting the position of immunological biomarkers regarding treatment and its prognostic approach in cancer cases. The knowledge regarding the analysis of T cell subsets is still not yet completely disclosed and studies undertaken are also few. From the studies undertaken till now it can be understood that immunosurveillance and immune cells plays a significant part in the development of the OSF and oral squamous cell carcinoma (OSCC). Taking this as background this review gives the essential role of T cells and their subsets to understand the detailed T cell profiling in OSF cases and OSCC in background of OSF such that a future hypothesis can be formulated to undertake research which can give the translational value.

Keywords: T cell subsets; oral submucous fibrosis (OSF); oral squamous cell carcinoma (OSCC); malignant transformation (MT)

Received: 12 January 2023; Accepted: 21 November 2023; Published online: 19 December 2023.
doi: 10.21037/fomm-23-5
View this article at: https://dx.doi.org/10.21037/fomm-23-5

Introduction

Over one billion people use tobacco products globally, and over 12% percent of deaths in people aged more than 30 years are attributed to tobacco use (1). Many studies have been done to analyze the effects of chewing tobacco on human body homeostasis; these studies include analyzing cancerous effects, toxicities, role in the induction of inflammatory microenvironments in various organs, and some basic analysis regarding the basic immune functions. Indian population has case-control reports which identify tobacco chewing as a menacing factor for many oral potentially malignant disorders (OPMDs) and oral cancer related to smoking and non-smoking tobacco (1,2).

Oral squamous cell carcinoma (OSCC) justifies around 90% of all neoplasms of oral malignancies, being the sixth most common globally (1). In a few South Asian countries

^ ORCID: 0000-0002-0481-2095.

including India, OSCC is still more predominant compared with others (2). This erraticism in the universal frequency of OSCC has seen to be accredited to social habits, counting the intake of tobacco, alcohol, and areca nut. These tumors are habitually confined, and exophytic, and are frequently related to vital immunosuppression chiefly in the progressive stage. Recent studies concerning the immune system have discovered about the host immune could affect tumor growth, accenting the position of immunological biomarkers regarding treatment and its prognostic approach in cancer cases (3,4). In about one-third of the cases, OSCC might occur by OPMD (5).

Oral submucous fibrosis (OSF) is a precancerous condition with marked alteration in fibers of connective tissue concerned with the lamina propria and its deeper position. In the period of about 10 years the OSF has shown 7.6% of the malignant transformation (MT) rate (6). In Indian countries OSF signifies a public health delinquent, with studies have been related to usage of areca nut, a known potentially carcinogenic entity; though, the mechanisms behind it could not be proven (2,7). The OSF linked with OSCC (OSF-OSCC) is known to be usual malignant neoplasm in areas of South and Southeast Asia (6). It appears that the OSCC developing from OSF and that arising from oral leukoplakia convey generally variable prognostic inferences. The immune system is also known to play the utmost significant part in the regulation of OPMD and frank invasive lesions.

The immune cell infiltrates seen in early OSF consists of neutrophils and eosinophils and in the later stage, lymphocytes and plasma cells are more which are of chronic types. It has also been studied that mast, macrophages, Langerhans' cells other than T cells also has part in the pertinence with immunomodulation in occurrence and development of OSF (8).

With the progress of time, it is getting very apparent that numerous subsets of T cells have a key part in the maintenance of body homeostasis. Several researchers are concerned about the T cell subset counts and functionality in various diseases, where research groups are trying to establish links between T cells profile and pathological symptoms or the predisposition for the disorders. The passable host immune response defends the mucosa from its malignant change of it (9). The knowledge regarding analyzed data of T cell subsets including T helper cell subgroups [Th1, Th2, Th17, and regulatory T cells (Tregs)], both for their percentages and functionalities and secondly, the profile analysis of studies based on the memory and readiness to combat infectious and cellular diseases (all subsets of memory cells) is required to understand the pathogenesis. Tobacco chewing harms the homeostasis of the body, generates an inflammatory situation, weakens the immune response, and makes the body prone to the onset of cancer is a well-known fact (10). Taking this as background this review gives the essential role of T cells and their subsets to understand the very detailed T cell profiling in OSF cases and OSCC in background of OSF. The databases like PubMed and Science Direct were searched under leading related keywords: "T cell subsets", AND "oral submucous fibrosis" AND/OR "oral squamous cell carcinoma", AND/OR "oral squamous cell carcinoma in background of oral submucous fibrosis", AND/OR "immune system".

Immune system and OSCC

The immune and inflammatory responses to OSCC are multifaceted and have significance in the advancement and disease prognosis. In the protection against cancer, the immune system has a major role, which was already made known at the start of 1970s itself by Noone and his co-researchers about the prognostic state of OSCC which got better if T lymphocytes were seen in tumor (11). The cancer immunosurveillance hypothesis states recognizing the cancer precursor cells by the immune system and destruction by them (12). Nevertheless, the recently presented idea of cancer immunoediting is directed as an impulsive interface in between the immune system and tumor or dysplastic cells, along with proper stages of eliminating, balancing, and escaping (11-13). An amplified amount of Tregs was noted with peripheral blood, lymph nodes, and tumor cells in cases of OSCC (14,15). The prognostic value was seen with the existence of tumor-infiltrating lymphocytes (TILs) which could reflect the response of the host immune towards tumor cells (16). Tregs are also required in maintaining the oral mucosa concerning immune tolerance. Though noted increased amount of Tregs in oral cancer, the consequence of this spectacle is controversial and their increase is connected to improvement in the OSCC prognosis. A better patient survival rate was noted in one study, which showed high in "$CD4^+$, CD25, and CD127" cells in early-stage OSCC associated with late-stage (17). The high levels of tumor-infiltrating Tregs were connected to the low rate of metastasis in lymph nodes, and higher entity of forkhead box P3 $(FOXP3)^+$ T cells were considerably connected with allover extended survival rate (18). Aggarwal *et al.*

also showed more Treg subsets with the progression of the tumor, with advanced cases and in large tumors and node involvement. Thus, all the above-mentioned studies give the inference of the increased occurrence of Treg cells must be contributory to the increased ratio of "$CD3^+$, and $CD4^+$ T cells" (19).

T cells and OSF

The immune system is also noted to regulate OPMD and even the lesions of frank invasive. The study done by Sirsat *et al.* on OSF tissue by different stains like hematoxylin-eosin, Mallory's trichome, etc. showed the presence of inflammatory cells within all the OSF stages. They found in the first stage predominantly polymorphonuclear leukocytes and occasionally eosinophils, in second stage mononuclear lymphocytes, eosinophils, and episodic plasma cells, and existence of lymphocytes and plasma cells pertaining to advanced and moderately advanced cases of OSF were showed (20).

Haque *et al*. [1997] established the infiltration of inflammatory cells in the OSF tissue which comprised mainly of T lymphocytes. They showed the activated $CD3^+$ T lymphocytes, $CD4^+$ helper/inducer T lymphocytes, and some dispersed $CD8^+$ suppressor/cytotoxic T lymphocytes. The casual infiltration of $CD20^+$ B lymphocytes and $CD68^+$ cells which belongs to macrophages and Langerhans' cells were found in tissues of OSF (21).

Haque *et al.* [1998] in their further research study on OSF inspected the existence and allocation of cells pertaining to inflammation and major histocompatibility complex (MHC) class II antigen representation with epithelium and cells of immunocompetent by immunoperoxidase method on frozen tissues (22). Antibodies to all T cell subsets (CD3, CD4, CD8, CD20), naive T cells and monocytes (CD45RA), macrophages, Langerhans' cells (CD68), positive human leukocyte antigen-DR cells (HLA-DR alpha) were investigated (23). Predominantly the CD3, CD4, and HLA-DR-positive cells found detected in OSF comparing with the control. Some of dispersed CD8-positive cells and just infrequent cells of CD20 and CD68-positive were reported in OSF. The existence of above-mentioned immunocompetent cells with higher proportion of CD4 to CD8 propose a continuing cellular immune event directing towards likely disparity of immunoregulation and architectural modification of the tissue (21,22).

Yet, the above referred studies are inferences based on qualitative investigation of inflammatory component in tissues of OSF, and quantitative analysis of it is still not reported for OSF tissues. Increased infiltration of activated lymphocytes in the epithelium and sub-epithelium specifies greater local inflammatory reaction and recommends amplified production of immunomodulatory cytokine. It is not even distinct that the type of CD4 cells (Th0, Th1-like, and Th2-like) are predominantly needed in OSF for releasing cytokines. Certain set of lymphocytes might give cytokines pertaining to antifibrosis, including IFN-7, due to the deficiency of HLA-DR countenance on cells of epithelium proposes that these particular cells might not be chiefly intricated in the pathology (21).

Analyzing quantitatively for the immunocompetent cells comparing moderately advanced and advanced OSF tissue discovered that the density of T lymphocytes and macrophages of the epithelium and in subepithelium was significantly high in advanced OSF (22). Activated form of T lymphocytes do not even generate cytokines of the fibrogenic variant that effects straight on connective tissue cells, and as well bring forth additional cytokines which activates macrophages for the secretion of fibrotic cytokines which moderate the purpose of mesenchymal cells implicitly (23). This can be related to the study done on inflammatory cells induced cytokines and growth factors which might endorse fibrosis by persuading propagation of fibroblasts (FBs), upregulation in synthesis of collagen, and downregulation of collagenase synthesis (22). Both the studies by Chiang *et al.* and Haque *et al.* presented augmented amount of T lymphocytes and macrophages activated form in the oral mucosal subepithelial portion of affected OSF cases. Captivating such outcomes altogether, can be accomplished about the cellular immune event with the raised formation of fibrogenic cytokines and decrease in antifibrotic cytokines that plays majorly in the OSF pathogenesis suggesting the higher density of T lymphocytes of epithelium in the OSF specimens compared to normal (22,23).

A higher level of phenotypic allele A6 of MHC class I chain-related gene A (MICA) in OSF is concomitant to the variation in T-cell action (24). Few genotypes of cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), which is negative regulator of T-lymphocyte activating factor appears to take a vulnerability for several autoimmunity which could be correlated with the OSF. Remarkably, the allele G at location +49 of exon 1 were instituted to be related with OSF related to controls (25). The CD68 in the affected cases of a moderate and advanced type of OSF was found high that of the controls with statistical significance.

Table 1 T cells subsets expression in OSF and OSCC arising from OSF studies

Cases	T cells subsets	Method	Sample type	Findings	Reference
OSF	Inflammatory cells—polymorphonuclear leukocytes, mononuclear lymphocytes, eosinophils, lymphocytes, and plasma cells	Hematoxylin-eosin, Mallorys trichome	Tissue sample	In very early stage polymorphonuclear leukocytes, late early-stage lymphocytes and eosinophils, and advance stage lymphocytes and plasma cells were noted	Sirsat *et al.* in 1967 (20)
	$CD3^+$ cells, $CD4^+$ cells, and $CD68^+$, $CD20^+$ and $CD68^+$	IHC	Tissue sample	CD3, CD4, and HLA-DR-positive cells were increased	Haque *et al.* in 1997 (21)
	CD3 and CD4, T lymphocytes. Langerhans' cells, MHC class II, HLA-DR	IHC	Tissue sample	CD3 and CD4 showed T lymphocytes. Langerhans' cells presenting dendritic structure and MHC class II expression, and lymphocytes depicting HLA-DR positive cells	Haque *et al.* in 1998 (22)
	T lymphocyte, B lymphocyte and macrophage density by $CD4^+$ and $CD8^+$ lymphocyte numbers	IHC	Tissue sample	Evidentially increased T lymphocytes and macrophages. Predomination of $CD4^+$ cells on $CD8^+$ cells in the subbasalar area	Chiang *et al.* in 2002 (23)
	MICA	Genotyping by PCR	Tissue sample	The phenotypically allele A6 of MICA frequency is high in OSF subjects compared to controls	Liu *et al.* in 2004 (24)
	CTLA-4, CD152	Genotyping by PCR	Peripheral blood sample	CTLA-4 +49 G allele bestows increase in frequency and probability of OSF	Shin *et al.* in 2004 (25)
	CD68	IHC	Tissue sample	CD68 significantly higher in OSF	Pereira *et al.* in 2015 (26)
OSF with OSCC	CD303, CD207, and CD1a	IHC	Tissue sample	The reduced amount of $CD1a^+$ and $CD207^+$ cells in OSF and OSF associated with OSCC, and increase in the $CD303^+$ cells	Silva *et al.* 2020 (5)

OSF, oral submucous fibrosis; OSCC, oral squamous cell carcinoma; IHC, immunohistochemistry; HLA-DR, human leukocyte antigen-DR isotype; MHC, major histocompatibility complex; MICA, MHC class I chain-related gene A; PCR, polymerase chain reaction; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4.

Which advocates that CD68 has a major part in OSF pathogenesis and could be observed as a major biomarker for evaluating the prognosis (26).

The study by Wang *et al.* on FBs by cytokine-containing supernatant which was co-cultured with human peripheral blood mononuclear cells (PBMCs), the cytometric analysis gave increase in Th17, but significant decrease in Treg. The arecoline may alter inflammatory cytokines given by FBs, which in turn show upon immune cells Th17 and Treg, and alteration is seen (27). The studies pertaining to T cell and OSF are listed down in *Table 1*.

T cell in OSCC with a background in OSF

OSCC arising in OSF make up a clinicopathologically outlined entity, the variances of that supposed to rise from disparity in the pathogenesis of areca nut carcinogenesis. Various studies were done on OSF about T cells and their subsets show the increase in the infiltration or the density of T cells depending on the various grades of OSF suggesting the disparity of immunoregulation and variation in tissue architecture locally and also inflammatory cells activate certain cytokines which are responsible for tissue fibrosis in OSF. The T lymphocytes and macrophages in active form affect the host immune cellular retort with the raised secretion of fibrogenic cytokines and reduction of antifibrotic cytokines with key pathogenesis factor of OSF (21-23).

Sarode *et al.* hypothesized about the MT of OSF, transforming epithelial malignant cells might hold the genetic

memory of earlier distinction and maturement ensuing in a better tumor differentiation stage (28). Silva *et al.* studied the immature dendritic cells (DCs), Langerhans' cells, and plasmacytoid DCs organization which recognize antigens and present to T cells in OSF, OSF-related with OSCC, and other OPMDs. They showed immunoreactivity was lower in positive CD1a and CD207 cells in both the entities of OSF and OSCC-OSF considered with comparison to the standard epithelium (5) (*Table 1*). The countenance in receptor CD207 in DCs signals the antigen is efficiently joined with MHC-I and MHC-II, a form that triggers the $CD8^+$ and $CD4^+$ T cells; so, this down-regulated receptor in DCs may designate a conquest of the response of T-cell. A steady upsurge in $CD303^+$ cells was detected for all the lesions of the study group. This increased value of $CD303^+$ cells may be connected to the defense part of the immune system. The decreased number of cells $CD1a^+$ and $CD207^+$ can subordinate in the growth of OSCC, and in OPMDs which will be pointers of prognosis to malignancy. This indicated about areca nut consumption might yield a more suppressing immune cell role (5).

Conclusions

Looking at the above studies it can be understood that immunosurveillance and immune cells play a significant role in the development of the OSF and OSCC. It can be advisable that assessing of OSF and cancer patients immunologically might give up early diagnosis and/or prognosis. The response of host immune T cells with their subsets creates great prognostic value as immune defense, especially in OSF, and can be considered as markers in malignant transformers which may be valuable for proactive intervention, particularly in high-risk groups. More studies can be undertaken to know in-depth pathogenesis and related pathways about T cells and OPMD. Taking this review as background it can be hypothesized that their can be essential role of T cell subsets in OSF and OSCC in background of OSF and in detail T cell profiling can prove the prognostic value.

Acknowledgments

Funding: None.

Footnote

Peer Review File: Available at https://fomm.amegroups.com/article/view/10.21037/fomm-23-5/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://fomm.amegroups.com/article/view/10.21037/fomm-23-5/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Kujan O, Mello FW, Warnakulasuriya S. Malignant transformation of oral submucous fibrosis: A systematic review and meta-analysis. Oral Dis 2021;27:1936-46.
2. Prasad J B, Dhar M. Risk of major cancers associated with various forms of tobacco use in India: a systematic review and meta-analysis. J Public Health 2019;27:803-13.
3. Almangush A, Mäkitie AA, Triantafyllou A, et al. Staging and grading of oral squamous cell carcinoma: An update. Oral Oncol 2020;107:104799.
4. Gnjatic S, Bronte V, Brunet LR, et al. Identifying baseline immune-related biomarkers to predict clinical outcome of immunotherapy. J Immunother Cancer 2017;5:44.
5. Silva LC, Fonseca FP, Almeida OP, et al. CD1a+ and CD207+ cells are reduced in oral submucous fibrosis and oral squamous cell carcinoma. Med Oral Patol Oral Cir Bucal 2020;25:e49-55.
6. Shih YH, Wang TH, Shieh TM, et al. Oral Submucous Fibrosis: A Review on Etiopathogenesis, Diagnosis, and Therapy. Int J Mol Sci 2019;20:2940.
7. More CB, Rao NR. Proposed clinical definition for oral submucous fibrosis. J Oral Biol Craniofac Res 2019;9:311-4.
8. Wang L, Tang Z. Immunopathogenesis of oral submucous fibrosis by chewing the areca nut. J Leukoc Biol

2022;111:469-76.
9. Pellicioli ACA, Bingle L, Farthing P, et al. Immunosurveillance profile of oral squamous cell carcinoma and oral epithelial dysplasia through dendritic and T-cell analysis. J Oral Pathol Med 2017;46:928-33.
10. Gonçalves RB, Coletta RD, Silvério KG, et al. Impact of smoking on inflammation: overview of molecular mechanisms. Inflamm Res 2011;60:409-24.
11. Noone RB, Bonner H Jr, Raymond S, et al. Lymph node metastases in oral carcinoma. A correlation of histopathology with survival. Plast Reconstr Surg 1974;53:158-66.
12. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6:715-27.
13. Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002;3:991-8.
14. Gaur P, Singh AK, Shukla NK, et al. Inter-relation of Th1, Th2, Th17 and Treg cytokines in oral cancer patients and their clinical significance. Hum Immunol 2014;75:330-7.
15. Schwarz S, Butz M, Morsczeck C, et al. Increased number of CD25 FoxP3 regulatory T cells in oral squamous cell carcinomas detected by chromogenic immunohistochemical double staining. J Oral Pathol Med 2008;37:485-9.
16. Hui L, Chen Y. Tumor microenvironment: Sanctuary of the devil. Cancer Lett 2015;368:7-13.
17. Spector ME, Bellile E, Amlani L, et al. Prognostic Value of Tumor-Infiltrating Lymphocytes in Head and Neck Squamous Cell Carcinoma. JAMA Otolaryngol Head Neck Surg 2019;145:1012-9.
18. deLeeuw RJ, Kost SE, Kakal JA, et al. The prognostic value of FoxP3+ tumor-infiltrating lymphocytes in cancer: a critical review of the literature. Clin Cancer Res 2012;18:3022-9.
19. Aggarwal S, Sharma SC, N Das S. Dynamics of regulatory T cells (T(regs)) in patients with oral squamous cell carcinoma. J Surg Oncol 2017;116:1103-13.
20. Sirsat SM, Pindborg JJ. Subepithelial changes in oral submucous fibrosis. Acta Pathol Microbiol Scand 1967;70:161-73.
21. Haque MF, Harris M, Meghji S, et al. An immunohistochemical study of oral submucous fibrosis. J Oral Pathol Med 1997;26:75-82.
22. Haque MF, Harris M, Meghji S, et al. Immunolocalization of cytokines and growth factors in oral submucous fibrosis. Cytokine 1998;10:713-9.
23. Chiang CP, Wu HY, Liu BY, et al. Quantitative analysis of immunocompetent cells in oral submucous fibrosis in Taiwan. Oral Oncol 2002;38:56-63.
24. Liu CJ, Lee YJ, Chang KW, et al. Polymorphism of the MICA gene and risk for oral submucous fibrosis. J Oral Pathol Med 2004;33:1-6.
25. Shin YN, Liu CJ, Chang KW, et al. Association of CTLA-4 gene polymorphism with oral submucous fibrosis in Taiwan. J Oral Pathol Med 2004;33:200-3.
26. Pereira T, Naik S, Tamgadge A. Quantitative Evaluation of Macrophage Expression Using CD68 in Oral Submucous Fibrosis: An Immunohistochemical Study. Ann Med Health Sci Res 2015;5:435-41.
27. Wang L, Gu L, Tang Z. Cytokines secreted by arecoline activate fibroblasts that affect the balance of TH17 and Treg. J Oral Pathol Med 2020;49:156-63.
28. Sarode SC, Sarode GS. Better grade of tumor differentiation of oral squamous cell carcinoma arising in background of oral submucous fibrosis. Med Hypotheses 2013;81:540-3.

doi: 10.21037/fomm-23-5
Cite this article as: Yadahalli R, Sarode GS, Sarode SC. T cell subset—an overview in oral submucous fibrosis and oral squamous cell carcinoma in background of oral submucous fibrosis. Front Oral Maxillofac Med 2023.