Original Article

Role of S100 A7 as a diagnostic biomarker in oral potentially malignant disorders and oral cancer

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Abstract

Background: S100 proteins have been implicated in the tumorigenesis of different human cancers and in oral dysplasia, as they are keratinocytes.

Materials and Methods: In the present study, we have attempted to compare the expression of S100-A7 within young-onset (age ≤45 years, Group 1) oral squamous cell carcinoma (OSCC), OSCC in older age groups (age >45 years Group 2), oral potentially malignant disorders (OPMDs, Group 3) and inflammatory lesions (Group 4). The tissue sections were scored based on the percentage of immunostained cells and staining intensity. Nuclear, cytoplasmic and membrane immunoreactivity were also scored.

Results: The present study comprised 153 histopathologically diagnosed case subjects of OSCC >45 years (n = 41), OSCC <45 years (n = 36), OPMD (n = 40) and inflammatory lesions (n = 36). The present study revealed a statistically significant difference of distribution with regard to S100A7 staining (cytoplasmic and nuclear) between OPMDs and OSCC ($P < 0.05$). The nuclear, cytoplasmic and membrane staining as well as the staining intensity had significantly different scoring patterns among the OSCC group, OPMD group and the inflammatory lesions with the OSCC group having the highest scoring of the S100A7 staining (irrespective of the age).

Conclusions: The present study concludes that S100A7 can be used as a diagnostic biomarker to differentiate between OPMDs and OSCC lesions. However, the marker is unable to distinguish between OSCCs in younger and older patients as the molecular pathogenesis of tumors in either of these age groups is probably similar.

Keywords: Biomarker, immunohistochemistry, oral potentially malignant disorders, oral squamous cell carcinoma

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the sixth most prevalent malignancy with an annual incidence of more than 275,000 cases worldwide. India is known to have one of the highest incidence in the world with

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over 100,000 cases/year.[1] Squamous cell carcinoma of the head and neck squamous cell carcinoma (HNSCC) is reported most commonly among older adults, occurring most frequently in patients older than the age of 45 years. Epidemiological studies over the last 20 years have shown a steady rise in the incidence of these cancers in younger adults (age 18–45 years), especially when they occur in the oropharynx and oral cavity.[2] Several etiological factors have been implicated in the initiation and progression of OSCC including tobacco intake, smoking, alcohol, dentition status, diet, oral hygiene, genetic predisposition[3,4] and more recently, human papillomavirus.[5] Literature indicates a controversy with regard to the difference in the etiology, clinical phenotypes and survival rate between the young and the old adults[6] with a few studies indicating a higher rate of distant metastasis and a worse prognosis in case of young patients.[7]

Oral carcinogenesis is believed to evolve as a multi-step process where the majority of OSCCs are thought to be preceded by or associated with potentially malignant lesions that may have the potential to transform into cancer. Accumulation of the genetic events which modify the signal transduction pathways and enhance the cell's ability for proliferation and invasion is represented histologically as the various oral potentially malignant disorders (OPMDs).[8] Despite the progress in the field of molecular biology, no single or a set of molecular markers can reliably predict the malignant transformation rates of OPMDs.

Several members of the multifunctional Ca2+ binding S100 proteins have been described in connection with a range of human cancers, including OSCCs, and differential expression of S100A7 has been described in different human cancers. S100-A7, a small calcium-binding protein of the S100 protein family, originally identified in psoriatic keratinocytes, is upregulated in abnormally differentiating keratinocytes, in squamous carcinomas of different organs and in a subset of breast tumor. Incidentally in a study, S100-A7 was also identified in oral premalignant epithelia by immunohistochemistry and proposed to be a marker for invasion.[9] Hence, the present study has attempted to elucidate and compare the differential expression of S100-A7 via immunohistochemistry among young-onset OSCC, OSCC occurring in older age group and patients with OPMDs in the Indian population. The study also aims to explore the association of S100A7 as a diagnostic marker in patients aged 45 years and younger reporting with OPMDs and OSCC.

MATERIALS AND METHODS

The present study was approved by the Research Ethical Board of All India Institute of Medical Sciences, New Delhi, before commencement. The study consists of 153 case subjects of Indian origin who reported to the Cente for Dental Education and Research, AIIMS, New Delhi, from January 2016 to December 2018. Following a detailed oral examination of the suspicious lesions, written informed consent was obtained from the subjects selected for the study.

Lesions having a diameter <5 mm were excised while in case of lesions >5 mm diameter, the area within the lesion which showed maximum suspicion for malignancy was biopsied and was subsequently evaluated via histopathological examination. Biopsy was performed from the most visually diseased site for all the cases which had either clinically frank cancer or suspicious for oral cancer/OPMD. Suspicious lesions included any ulcerative lesion lasting for more than 2–3 weeks, leukoplakia >2 cm in size, nonhomogeneous leukoplakia/nodular/speckled leukoplakia, lesion on tongue and floor of mouth, leukoplakia not associated with tobacco/areca nut habit (idiopathic leukoplakia), verrucous lesions, lichenoid lesions, any long-standing leukoplakia exhibiting changes in surface texture, color, size, contour deviation, loss of mobility of intraoral or extraoral structures, loss of surface integrity and no or minimal/partial response to therapy. Biopsy tissue was collected in 10% formalin and embedded in paraffin for histopathological and immunohistochemical analyses.

Inclusion criteria

Case subjects who were histopathologically diagnosed as OSCC or OPMD.

Exclusion criteria

Subjects with a history of any known systemic disease, other concurrent tumors, metastatic cancers, cancers of the salivary glands, nasopharynx and hypopharynx or the ones which refused participation were excluded from the study.

Establishment of clinical and histopathological diagnosis by pathologists (DM, AS and SDG) was performed in accordance with the guidelines by the WHO Classification of Head and Neck Tumors 2017 following which the case subjects were divided into four groups, i.e.,

- Group 1: Patients diagnosed with OSCC of age more than 45 years (graded as well, moderately and poorly differentiated squamous cell carcinoma [SCC], sarcomatoid SCC)
- Group 2: Patients diagnosed with OSCC of age 45 years or younger

- Group 3: Patients diagnosed with OPMD disorders comprising histologically diagnosed as mild, moderate, severe dysplasia, epithelial hyperplasia, hyperkeratosis, oral lichen planus, oral submucous fibrosis and verrucous hyperplasia
- Group 4: Comprised inflammatory lesions group, i.e., the case subjects which never had OPMD or cancer (comprising inflammatory lesions such as pericoronitis and fibrous hyperplasia).

Patient demographic, clinical and pathological data were recorded in a predesigned pro forma as described previously.[6] The information documented included clinical tumor, node and metastasis (TNM) staging (TNM based on the Union International Centre of Cancer TNM Classification of Malignant Tumors 2002), site of the lesion, histopathological differentiation, age, gender and tobacco consumption habits.

Immunohistochemistry

S100A7 expression was evaluated among four groups consisting of histologically confirmed oral normal epithelia, epithelial hyperplasia, dysplasia and OSCC through immunohistochemistry. Paraffin-embedded sections (3 μ) of human OPMDs, OSCC and inflammatory lesions were collected on silane-coated slides. The sections were deparaffinized in xylene, hydrated in gradient alcohol and pretreated in a microwave oven for 10 min at 800 W and 5 min at 480 W in citrate buffer (0.01 M, pH = 6.0) for antigen retrieval. The sections were incubated with hydrogen peroxide (0.3% v/v) in methanol for 30 min to quench the endogenous peroxidase activity, followed by blocking with 1% bovine serum albumin to preclude nonspecific binding. Thereafter, the slides were incubated with mouse monoclonal anti-S100A7 antibody (0.5 ug/ml, for 16 h at 4°C. Detection of primary antibody was done using the streptavidin–biotin complex with the Dako LSAB Plus Kit (Dako Cytomation, Glostrup, Denmark) and diaminobenzidine as the chromogen. In the negative control tissue sections, the primary antibody was replaced by isotype-specific nonimmune mouse immunoglobulin G. A section from estrogen receptor-negative breast cancer tissue was used as a positive control in each batch of immunohistochemistry.

Evaluation of immunohistochemical staining

Immunostaining was performed on whole-tissue sections and slides were evaluated by three independent pathologists (DM, AS and SDG). Discordant cases were re-evaluated collegially. The stained slides were viewed at low magnification to identify areas potentially containing the greatest number of positive cells. Ten high power fields (×400 magnification) were then counted in these areas. Sections were scored as positive for that antibody when at least one cell nucleus, cytoplasm or membrane immunoreactivity was observed per high-power field. The percentage of positive tumor cell nuclei were evaluated approximately by visual scanning of the slides at medium power. The tissue sections were scored based on the percentage of immunostained cells as: 0%–10% =0; 11%–30% =1; 31%–50% =2; 51%–70% =3 and >70% =4. Sections were also scored on the basis of staining intensity as negative = 0; mild = 1; moderate = 2 and intense = 3. Finally, a total score was obtained by adding the score of percentage positivity and intensity.

Statistical analysis

Statistical analysis was performed using software IBM SPSS Statistics Version 21 (IBM, Tokyo, Japan). To test the hypothesis that the S100A7 expression will be affected by the histopathological diagnosis, Kruskal–Wallis one-way analysis of variance (ANOVA) was performed as the data generated was nonparametric. The level of significance was set at 0.05. If there was a statistically significant result obtained using the Kruskal–Wallis ANOVA, a Games–Howell *post hoc* test was performed to assess for specific intergroup differences.

RESULTS

The present study comprised 153 case subjects which were divided into four groups on the basis of histopathological evaluation: Group 1: OSCC detected at age >45 years (n = 41), Group 2: OSCC detected at age ≤45 years (n = 36), Group 3: patients with OPMDs (n = 40) and Group 4: inflammatory lesions (n = 36). One hundred and twenty-one case subjects were males (80%) and 31 case subjects were females (20%) [Table 1]. OPMD comprised maximum cases of leukoplakia followed by erythroplakia and oral submucous fibrosis. The present study revealed a statistically significant difference of distribution with regard to the staining parameters when assessed using ANOVA ($P < 0.05$). S100A7 staining (cytoplasmic and nuclear) was found to have a statistically significant difference between OPMDs and OSCC irrespective of age. When further using with the Games–Howell *post hoc* test, the nuclear, cytoplasmic and membrane staining as well as the staining intensity had statistically significant different scoring patterns among the OSCC group, OPMD group and the inflammatory lesions with the OSCC group (irrespective of the age) having the highest scoring of the S100A7 staining [Figure 1 and Tables 1-3]. No significant difference was found in the staining distribution between the Group 1 and Group 2 of OSCC with regard to other parameters.

DISCUSSION

The interplay between the malignant cells and the tumor microenvironment determines the growth, invasiveness and the metastatic potential and altogether plays a deterministic role in the prognosis of a tumor.[10] The members of the S100 family are multifunctional participating in a wide variety of cellular processes ranging from maintenance of cell shape and contraction, cell growth and differentiation, cell cycle progression, transcription, structural organization of membranes, calcium homeostasis, protein phosphorylation and secretion. They form the largest family of calcium-binding EF-hand (helix E-loop-helix F) signaling proteins and are soluble in 100% saturated ammonium sulfate solution, thus deriving their name from this particular property. First identified in 1965, these genes are found exclusively in vertebrates.[11]

The present study revealed a statistical significant difference of distribution with regard to the staining parameters between the OSCC, OPMD and the inflammatory lesions groups with the OSCC tissues showing an increased intensity of the S100A7 antibody, thereby indicating its use as a diagnostic marker for malignant transformation. Similar results with regard to the nuclear staining have been demonstrated in the immunohistochemical study by Tripathi *et al*. whereby a conclusion was drawn in favor of the nuclear S100A7 as having potential for predicting poor prognosis in head-and-neck squamous cell carcinoma (HNSCC) cases.[12] With regard to the nuclear staining, the present study revealed significant increased staining in Group 1 (OSCC in older patients) when compared with both the inflammatory lesions and OPMD case subjects ($P = 0.000$) with the mean difference being 1.0976 and 0.9476 respectively. However when compared to the Group 2, i.e., OSCC <45 years, there was no significant difference with regard to the nuclear staining. It is also to be noted that Mandal *et al*. in 2004 proposed that S100A7 plays an integral role in the acquisition of anoikis resistance in the oral cancer cells via their work on the Tu167 anoikis-sensitive cell lines and the mouse orthotopic models.[13] Anoikis has been described in literature as the apoptosis induced by lack of proper cell/extracellular matrix attachment. It brings forth the importance of the anchorage, epithelial–mesenchymal transition and cancer immortalization, especially in the epithelial and the endothelial cells which appear to be anoikis sensitive.[14] The same has been reiterated by Dey *et al*. who reported upregulation of S100A7 in anoikis-resistant cell lines, orthotropic model, biopsy samples as well as saliva of head-and-neck cancer patients. S100A7 can be a useful

Table 1: Description of baseline characteristics of the patients enrolled in the study

Clinical pathological features	Total cases	Nuclear staining, *n* (%)	*P*	OR (95% CI)	Cytoplasmic staining, *n* (%)	*P*	OR (95% CI)	Membrane staining, *n* (%)	*P*, OR (95% CI)	OR (95% CI)
OSCC (>45 years)	41	23 (56.1)	<0.001*	*	34 (82.9)	<0.001*	82.5 (15.9-426.4)	29 (70.7)	<0.001*,#	*
OSCC (≤45 years)	36	21 (58.3)		*	34 (94.4)		289 (38.4-2171.5)	27 (75.0)		*
OPMD	40	4 (10)		*	21 (52.5)		18.7 (3.9-88.9)	8 (20.0)		*
Inflammatory lesions	36	0 (0)		*	2 (5.6)		1	0 (0)		*
Gender										
Male	122	43 (35.2)	0.041	0.3 (0.12-0.98)	80 (65.5)	0.002	0.2 (0.12-0.65)	57 (46.7)	0.01	0.3 (0.13-0.82)
Female	31	5 (16.1)			11 (35.5)			7 (22.5)		
Age (mean±SD) (years) staining present	40	46±12.7	0.018	1.02 (1.004-1.05)	44.1±13.2	0.19	1.01 (0.99-1.03)	46.9±13.3	0.003	1.03 (1.01-1.05)
Staining absent	105	41.0±14.1			41.0±16.1			39.9±14.7		
Habits										
Nontobacco consumer	30	8 (26.7)	0.536	1.3 (0.54-3.23)	14 (46.6)	0.111	1.9 (0.85-4.25)	9 (30)	0.143	1.8 (0.80-4.45)
Tobacco consumers$	123	40 (32.5)			77 (62.6)			55 (44.7)		
Histological differentiation										
Well	21	17 (80.9)	0.03	1	19 (90.5)	0.99	1	17 (80.9)	0.809	1
Moderate	51	25 (49.0)		0.2 (0.06-0.76)	45 (88.2)		0.7 (0.14-4.26)	36 (70.6)		0.5 (0.16-1.96)
Poor	4	2 (50.0)		0.2 (0.02-2.21)	4 (100)		-	3 (75.0)		0.7 (0.05-8.69)

*Significant difference of distribution in S100A7 staining (cytoplasmic, nuclear and membrane) as well as the staining intensity among the OSCC group, OPMD group and the inflammatory lesions, with the OSCC group having the highest scoring (irrespective of the age), #OR cannot be calculated as none of the inflammatory lesions showed nuclear staining, $P < 0.05$ were considered statistically significant. OR: Odds ratio, CI: Confidence interval, OPMD: Oral potentially malignant disorders, OSCC: Oral squamous cell carcinoma, SD: Standard deviation

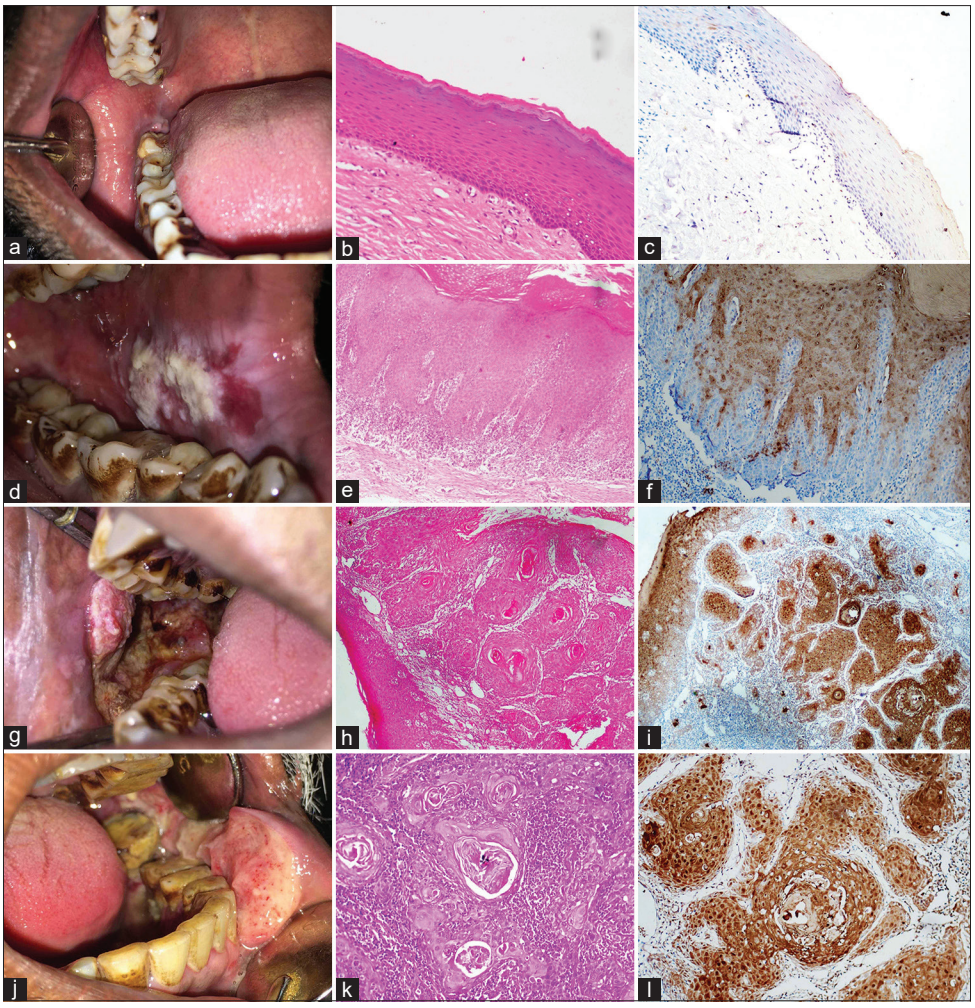

Figure 1: Clinical photograph, photomicrograph of hematoxylin and eosin-stained sections and immunohistochemical analysis of S100A7 in inflammatory lesions (fibrous hyperplasia) (a-c), oral potentially malignant disorders (d-f), oral squamous cell carcinoma (<45 years) (g-i) and oral squamous cell carcinoma (>45 years) (j-l)

diagnostic marker for early detection of primary cancers and is thought to be acting via RAB2A-MAPK pathway.[15]

While data exist in the published English literature with regard to the clinicopathological spectrum of the young oral cancer patients,[16-18] there is a glaring paucity of the data in relation to their defining biochemical, immunohistochemical or genetic markers if any. Most of the published literature indicates an increased incidence of oral and oropharyngeal carcinoma in young adults, with the most commonly affected site being the tongue in young patients. A recent analysis of the risk factors in oral tongue cancer patients revealed that the young patients (<45 years) were more likely to be female without a history of tobacco usage.[19] In addition, McGrady and Pai in a recent systematic review has suggested that 21%–60% of the adolescents and young cancer patients are liable to display poor conformity (nonadherence) to the cancer treatment protocols, hence exposing them to poor outcomes.[20] In this regard, Knopf *et al.* have attempted to elucidate the genes involved in the SCC of tongue in 276 young patients (<45 years) via immunohistochemistry and increased expression of CTNNB1, STK11, CDKN2A, HGF, MET along with the increased expression of radiosensitizers ATM, BRCA1E2F1 and FHIT.[21] Considering these factors, it becomes important to ascertain the differences between the young and the old cancer patients as well as to explore the various biomarkers that might be able to illuminate the hitherto occult differentiating molecular pathways between the two groups.

With regard to the cytoplasmic staining, the present study revealed significantly increased staining in the OSCC >45 years when compared with both the inflammatory lesions ($P < 0.0001$) and OPMD case subjects ($P = 0.024$), with the mean difference being 1.9185 and 0.8506, respectively. However, when compared

Table 2: Detailed distribution of histopathologically diagnosed cases of oral squamous cell carcinoma and oral potentially malignant disorders according to their S100A7 positivity

	Cases with OSCC ≤45 years	Cases with OSCC >45 years	OPMD (OSMF, epithelial hyperplasia, OLP, verrucous hyperplasia, epithelial dysplasia)	Inflammatory lesions (pericoronitis, fibrous hyperplasia)
S100A7 positive	34 (82.9)	34 (94.4)	22 (55.0)	2 (5.56)
S100A7 negative	7 (17.07)	2 (5.56)	18 (45.0)	34 (94.44)
Total	41	36	40	36

OPMD: Oral potentially malignant disorders, OSCC: Oral squamous cell carcinoma, OLP: Oral lichen planus

Table 3: Biomarker analysis of S100A7 (nuclear/cytoplasmic/membranous) in all the groups

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)	Area under curve
Nuclear staining						
Inflammatory lesions versus OPMD	100	50	10	100	52.63	0.66
Inflammatory lesions versus OSCC (>45 years)	100	70.59	58.33	100	79.17	0.79
Inflammatory lesions versus OSCC (≤45 years)	100	66.67	56.1	100	76.62	0.78
Cytoplasmic staining						
Inflammatory lesions versus OPMD	91.3	64.1	52.5	94.4	72.37	0.82
Inflammatory lesions versus OSCC (>45 years)	94.4	94.4	94.4	94.4	94.4	0.96
Inflammatory lesions versus OSCC (≤45 years)	94.4	82.9	82.9	94.4	88.31	0.90
Membranous staining						
Inflammatory lesions versus OPMD	100	52.94	20	100	57.89	0.72
Inflammatory lesions versus OSCC (>45 years)	100	80	75	100	87.5	0.87
Inflammatory lesions versus OSCC (≤45 years)	100	75	70.73	100	84.4	0.85

OPMD: Oral potentially malignant disorders, OSCC: Oral squamous cell carcinoma, PPV: Positive predictive value, NPV: Negative predictive value

to the Group 2, i.e., OSCC <45 years, there was no significant difference with regard to the cytoplasmic staining. Interestingly, Kaur *et al.* in their study indicated reduced oral cancer-free survival in patients exhibiting increased cytoplasmic S100A7 immunostaining.[9] Thus, we hypothesize that the final molecular pathway for tumorigenesis is similar in older and younger OSCC patients.

With regard to the membrane staining, the present study revealed significantly increased staining in the OSCC >45 years when compared with both the inflammatory lesions ($P < 0.0001$) and OPMD case subjects ($P = 0.024$), with the mean difference being 1.4390 and 1.0890, respectively. However, when compared to the Group 2, i.e., OSCC <45 years, there was no significant difference with regard to the cytoplasmic staining. To the best of our knowledge, this is the first study in the literature to report increased membrane immunostaining for S100A7.

Increased expression of S100A7 (psoriasin) has been associated with cancers of breast,[22] lung,[23] bladder,[24] skin,[25] pancreas,[26] stomach[27] and head and neck.[9,12] S100A7 has been shown to induce proliferation while suppressing squamous differentiation in SCCs. This is supported by the fact that S100A7 is located within a gene cluster in chromosome 1q21, known as the epidermal differentiation complex.[28] The increased expression of S100A7 in OSCC and OPMDs is not just limited to the tissues but can be identified in the saliva as well, as demonstrated by few recent studies.[29] Thus, we hypothesize that S100A7 can act as a promising biomarker in identifying the high-risk OPMD lesions in terms of their potential for malignant transformation which is consistent with the previous literature.[9,30]

CONCLUSION

The present study concludes that S100A7 can be used as a diagnostic marker in OPMDs and OSCC patients. However, the marker is not able to distinguish the group of oral cancer patients with young-onset disease.

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Conflicts of interest
There are no conflicts of interest.

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