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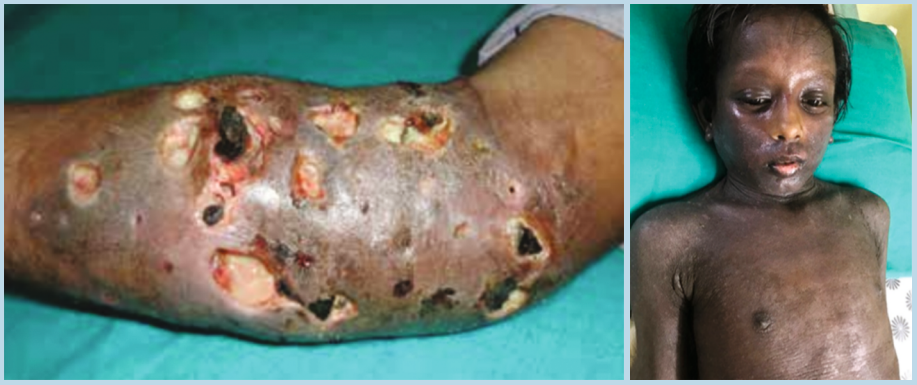

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ORIGINAL ARTICLE

Elevation of Serum SSCCAII in Cutaneous and Oral Lichen Planus: Missing Link for Hidden Carcinogenic Potential?

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Abstract

Context: Lichen planus (LP) is an immune mediated inflammatory condition. SCCAII is a useful biomarker reflecting Th17 type inflammation. It is also a tumour marker, especially for Squamous cell carcinoma (SCC) Mechanism of carcinogenesis in LP is still unknown. Chronic inflammation may facilitate the development of cellular clones in the epidermis. **Aims:** Estimation of serum level of SCCA II in patients with cutaneous and oral LP (OLP) to detect its role in LP pathogenesis, and to reveal the missing link in understanding mechanism of carcinogenesis in LP. **Methods and Material:** A case control study, where 100 subjects were included; 80 LP patients (40 cutaneous & 40 oral) and 20 apparently healthy controls. We obtained an informed written consent from each subject prior the participation. Cutaneous and oral LP were diagnosed clinically, SCCA II level was measured by ELISA technique. **Statistical analysis used:** Statistical analysis was done using SPSS vs.25. (IBM, Armonk, New York, United states). Numerical data was summarized as means and standard deviations or medians and ranges. **Results:** Median SSCCAII level was significantly higher in LP cases compared to controls ($P < 0.001$) and was significantly higher in patients with OLP compared to patients with cutaneous LP ($P \leq 0.001$). Post hoc analysis revealed that median SSCCAII was significantly higher in patients with ulcerative type compared to both reticular type and others. It was also significantly higher in patients with actinic type compared to both hypertrophic type and classic type. Median SSCCAII was significantly higher in patients with ulcerative OLP compared to actinic LP ($P < 0.001$). **Conclusions:** Our study revealed that serum SCCAII level was higher in patients with cutaneous and OLP. This might be linked to the pathogenesis of LP, especially actinic and erosive OLP. SCCAII level could facilitate the screening and early detection of patients at risk, a potential alarm to launch accurate assessment and continue follow up of cutaneous as well as O LP patients.

Key Words: *Lichen planus, Squamous cell carcinoma antigen and Squamous cell carcinoma*

Introduction

Lichen planus (LP) is a T-cell-mediated condition with itchy, noninfectious lesion. The prevalence of LP is less than 5% without evident sexual predilection. Neoplastic transformation of cutaneous LP can occur and need to be kept in mind while treating nonhealing longstanding lesions.[1] The mechanisms of neoplastic changes in LP are unknown. Although frequently pronounced causes are idiopathic, arsenic exposure and radiation has been implicated as threat elements. Not surprisingly, the disease chronicity also has been considered as a hazard determinant of malignant behavior.[2] Chronic inflammatory processes with oncogenic growth factors may facilitate the development of cellular clones in the epidermis.[3]

The squamous cell carcinoma antigen (SCCA) belongs to ovalbumin-serpin proteinase inhibitor family,[4] SCCA is expressed in the spinous and granular layers of normal squamous epithelium in tongue and skin.[5] SCCAII is strongly induced by T-helper (Th) 17 type cytokines in keratinocytes and hence considered a useful biomarker

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reflecting Th17 type inflammation[6]- It is widely used as a tumor marker, particularly for SCC.[7] Elevated SCCA was observed not only in cutaneous malignancies but also in several skin diseases such as atopic dermatitis, eczema, pemphigus, erythroderma, and psoriasis.[8]

The pathogenesis of LP and SCC seems closely related.[9] Persistent antigenic stimulation by drugs, viruses as hepatitis and contact allergens resulting in chronic inflammatory process has been implicated in the development of malignancy.[10] Also, pruritus and scratching may also play a role in carcinogenesis.[11]

Materials and Methods

Study population

This cross-section case-control study included 100 participants—40 patients suffering from oral lichen planus and 40 patients suffering from cutaneous lichen planus, in addition to 20 apparently healthy controls. A written informed consent was obtained from all participants. This study was approved by Faculty of Medicine related local ethics committee on research of humans. This protocol of research work was in accordance with Helsinki declaration of the human rights.

All patients enrolled in the study were diagnosed clinically with cutaneous or oral lichen planus. Subjects with known history of malignancy, medical illness, and any dermatological disease other than LP were excluded from the study.

Laboratory tests

Five milliliters of venous blood were collected from all patients and controls under aseptic conditions by venepuncture. Samples were allowed to clot for 10–20 minutes at room temperature and centrifuged at 2000–3000 rpm for 20 minutes. Separated sera were immediately stored at – 80°C until analysis.

Serum SCCAII assay

Human (SCCAII) ELISA kit, a quantitative test kit double–antibody sandwich technique, from Sun Red Biotechnology Company, made in Shanghai, catalog NO (201-12-1657) with assay range (0.1 ng/ml → 30 ng/ml). It was performed on Das plate washer serial number (834) made in Italy and the result was obtained by Das plate reader serial number (1812) made in Italy.

Statistical analysis

Data management and statistical analysis were done using SPSS vs. 25. (IBM, Armonk, New York, United states). Numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Comparisons between cases and controls were done using Mann Whitney U test for numerical data. Categorical data were compared using Chi-square test or Fisher's exact test. Comparisons between oral and cutaneous lesions were done using independent *t* test or Mann Whitney U test for normally and non-normally distributed numerical variables, respectively. Categorical data were compared between oral and cutaneous lesions using Chi-square test or Fisher's exact test if appropriate. SSCCAII was compared as regard different parameters within cases (either OLP or cutaneous LP) using Mann Whitney U test. It was also compared between different morphologies using Kruskal Wallis test. *Post hoc* was done and all *post hoc* were Bonferroni adjusted. Correlation analysis was done between SSCCAII and other parameters using Spearman's correlation. "r" is the correlation coefficient.

Results

Median SSCCAII level was significantly higher in LP cases compared to controls ($P < 0.001$) and was significantly higher in patients with OLP (ranged from 1 ng/ml to 12.8 ng/ml) compared to patients with cutaneous LP (ranged from 1.02 ng/ml to 13.4 ng/ml) ($P \leq 0.001$) [Table 1].

SSCCAII level showed overall significance between patients with different morphologies of OLP ($P < 0.001$). *Post hoc* analysis revealed that median SSCCAII was significantly higher in patients with ulcerative type compared to reticular type and others. There was no significant difference between reticular type and others [Table 2]. Serum SCCAII level showed overall significant difference in SCCAII between patients with different morphologies of cutaneous LP ($P < 0.001$). *Post hoc* analysis revealed that median SSCCAII was significantly higher in patients with actinic type compared to both hypertrophic type and classic type. There was no significant difference between hypertrophic type and classic type [Table 3]. Median SSCCAII was significantly higher in patients with ulcerative oral LP compared to actinic LP ($P < 0.001$) [Table 4].

SSCCAII showed significant positive correlation in oral and cutaneous types with duration ($r = 0.748$ and $P < 0.001$ and $r = 0.776$ and $P < 0.001$, respectively) and were significantly higher in patients with progressive course (5 ng/ml and 2.17 ng/ml, respectively) compared to patients with stationary course (1.5 ng/ml and 1.12 ng/ml, respectively) ($P < 0.001$ each). There was no significant correlation with age, sex, and smoking. In oral lichen SSCCAII showed significantly higher level in patients with positive HCV Ab (9.34 ng/ml) compared to those with negative HCV Ab (2.96 ng/ml) ($P < 0.001$).

Discussion

In the current study, SSCCAII level was significantly higher in LP cases compared to controls ($P \leq 0.001$). This

Table 1: SSCCAII level in in patients, control, oral, and cutaneous types of LP

Head	Subjects	Cases (*n*=80)	Controls (*n*=20)	*P*	Oral LP (*n*=40)	Cutaneous LP (*n*=40)	*P*
SSCCAII (ng/ml)	Median (range)	2.22 (1-13.4)	1.44 (1.02-2.82)	0.004	3.75 (1-12.8)	1.71 (1.02-13.4)	0.001

Mann Whitney U test was used

Table 2: SSCCAII levels according to morphology in OLP

Head	Cases of L.P	Ulcerative (*n*=25)	Reticular (*n*=9)	Others (*n*=6)	*P*
SSCCAII (ng/ml)	Median (range)	6.23 (2.05-12.8)[a]	1.8 (1.33-2.91)[b]	1.15 (1-2.2)[b]	<0.001

Kruskal Wallis test was used. *Post hoc* was done and different letters indicate significant pairs. All *post hoc* comparisons were Bonferroni adjusted

Pair	*P*
Ulcerative vs. Reticular	<0.001
Ulcerative vs. others	<0.001
Reticular vs. others	1

Table 3: SSCCAII levels according to morphology in cutaneous LP

Head	Cases of L.P	Actinic (*n*=16)	Hypertrophic (*n*=8)	Classic (*n*=16)	*P*
SSCCAII (ng/ml)	Median (range)	3.01 (2.17-13.4)[a]	1.13 (1.05-1.24)[b]	1.58 (1.02-2.24)[b]	<0.001

Kruskal Wallis test was used. *Post hoc* was done and different letters indicate significant pairs. All *post hoc* comparisons were Bonferroni adjusted

Pair	*P*
Actinic vs. Hypertrophic	<0.001
Actinic vs. classic	<0.001
Hypertrophic vs. Classic	1.0

result might be explained by inflammatory cytokines, Th 17 axis in cutaneous, and OLP that induces SCCAII expression.[12,13] Interleukin (IL)-23, 17A, and 22 are the chief cytokines that orchestrate the Th17 pathway.[14] SCCA may be easily inducible from keratinocytes under inflammatory Th2 and Th17-type. The Th17 cytokines, IL-17, and IL-22, may induce higher SCCAII in serum.[6] SCCA may play some roles in type 2 immunity, and that it might be useful as a biomarker in related clinical contexts.[15]

Elevated SCCA was observed not only in malignancies of skin, esophagus, lung, anal canal, and vulva but also in many benign conditions, including lung tuberculosis, sarcoidosis, and skin diseases. In addition to being a tumor biomarker, SCCA has been increased in many skin conditions as atopic dermatitis, eczema, Psoriasis, pemphigus, and erythroderma as it was significantly higher in erythroderma caused by psoriasis than that caused by dermatitis, drug reactions, pityriasis rubra pilaris, and unknown causes.[16,17]

The SCCAII also may be linked to malignant behavior of LP so SCCAII should be considered a sensitive predictor for early malignant behavior in LP cases. Malignant transformation in LP is complicating between 1% and 15% of OLP and rarely cutaneous LP.[18] The incidence of SCC complicating cutaneous LP is 0.4%.[1] Du Castell,[19] reported first case of SCC arising in cutaneous LP, since then a further 74 cases have been described; however, the association between cutaneous, non-OLP, and SCC remain controversial. LP is considered a premalignant lesion. Premalignant lesions do not necessarily progress to malignancy.[20] Cutaneous LP is a premalignant condition with a low potential for malignant transformation.[18] The development of SCC has been attributed to chronic inflammation and accelerated cellular turnover in LP.[21] Pathogenesis of LP and SCC is closely linked.[9]

Although this study showed that higher levels of SSCCAII in patients with cutaneous LP, many studies showed that the risk of cancer was not increased in cutaneous LP. A study made by Sigurgeirsson *et al*.,[2] indicated that patients with cutaneous LP do not carry an increased risk of malignant transformation. However, Zargaran,[22] declared that LP patients are at risk of its transformation to SCC. There is enough evidence that chronic inflammation *per se* is able to provide a cytokine-rich media which will be able to influence cell survival and proliferation so contributing to cancer initiation and progression.[23] Chronic inflammatory condition is a known factor at the interface between genetics and the environment that contribute to carcinogenesis.[24] Chronic irritation and inflammation in

Table 4: Comparison between SSCCAII level in ulcerative oral LP and actinic LP

		Ulcerative oral lichen (n=25)	Actinic cutaneous lichen (n=16)	P
SSCCAII (ng/ml)	Median (range)	6.23 (2.05-12.8)	3.01 (2.17-13.4)	0.002

Mann Whitney U test was used

the form of itching and longstanding nonhealing lesions of LP, have been considered as triggering factor for an oncogenic-like overdrive of growth factors that stimulate the epithelial neoplastic transformation.

Although this study found that SCCAII was significantly higher in patients with actinic type compared to both hypertrophic type and classic type; Knackstedt *et al.*,[25] found that SCC occurs predominantly in hypertrophic LP. However, the precursor of most cutaneous invasive SCC is intraepithelial (ultraviolet) UV-induced damage, known as field cancerization,[26] SCC risk factors are radiation exposure and ultraviolet rays.[27,28] High expression of SCCA in UV-irradiated epidermis was observed and UV-induced apoptosis or UV-induced skin damage was decreased in SCCAI/II-overexpressed fibroblasts, knockdown of SCCAI in keratinocytes increased sensitivity to UV-induced apoptosis. Moreover, they showed that SCCAI inhibited JNK activity by binding to JNK and translocating to the nucleus, which was compatible with their finding that SCCAI was strongly stained in nuclei as well as cytoplasm in some UV-irradiated epidermis. This could be a mechanism of anti-apoptosis by SCCAI in keratinocytes exposed to UV.[29] UVB-associated inflammation is marked by myeloid infiltration, angiogenesis, and keratinocyte hyperproliferation in a toll-like receptor 4 (TLR4)-dependent play a critical role in early SCC development.[30]

Biopsied and sequenced populations of sun exposed yet normal-appearing human eyelid skin, showed high frequencies of numerous mutations previously observed in cutaneous SCC, including TP53, NOTCH1, and FAT1.[31] The SCCA was reported to inhibits UV-induced apoptosis via suppression of c-Jun NH2-terminal kinase[32] and PUVA treatment of LP have been implicated as potential promoters for malignant transformation of LP.[18]

SSCCAII level was significantly higher in patients with OLP compared to cutaneous LP ($P \leq 0.001$). This result can be explained by the studies proved that SCC can arise from biopsy-proven OLP as well as from unaffected mucosa.[33] Van der Meij *et al.*,[34] found that 34% of cases have evidence of malignant transformation of OLP. These data indicate not only a need for criteria or marker to establish a firm diagnosis of OLP but also a possible premalignant nature of OLP. The correlation between high SSCCAII level and malignant risk of OLP of 13,100 women in Finland and found that LP was associated with an increased risk of cancer of lip, tongue, and oral cavity.[35]

In agree with Sun and Chiang who showed that the serum SCCAII levels in some patients with major type ulcerative LP were significantly higher than other subjects. Carcinomas are more frequent in erosive OLP.[33] SSCCAII was significantly higher in patients with ulcerative type compared to both reticular type and others. This result can be explained by a systematic review made by Giuliani on the rate of malignant transformation of oral LP and it was found that ulcerative type of OLP should be considered as a risk factor for malignant transformation.[36]

Limitations

The limitation of the study was the need to strictly follow up and the sequential biopsies to detect early malignant changes and correlate results with the quantitative assessment of SCCA II levels.

Conclusion

Our study revealed that SCCAII level was higher in serum of cutaneous and oral LP patients than controls; a finding that may be linked to the pathogenesis of LP, inflammatory processes of Th17-type, or it may possibly represent a mechanism for malignant behavior especially in erosive oral and actinic types of LP. These results highlight the need to be aware of the suspicious changes in long-standing LP (especially actinic and erosive forms) to facilitate early detection of a developing SCC.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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This were an authors' own work. Laboratory investigations were done in clinical pathology laboratory.

Conflicts of interest

There are no conflicts of interest.

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