Original Article:

Association of serum IL-23 and IL-17A level with lichen planus: A case-control study

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Abstract

Background: Cellular involvement in the pathogenesis of lichen planus is well established. Initially it is mediated by T-helper 1 (Th1) response and in the later part it turns into a T-helper 2 (Th2) response. In the etiopathogenesis of lichen planus IL-17A and IL-23 may exert a crucial effect and discovering their role may help to emerge new therapeutic options to ameliorate disease symptoms and also complications like metabolic syndrome and malignancy. **Objectives:** To assess serum level of IL-17A and IL-23 in patients with lichen planus and healthy individuals by ELISA and to observe their association with disease severity. Methods: Patient of lichen planus was included as case and age and sex matched healthy individual as control were selected. 3 ml of blood sample was collected from both case & control for ELISA. Disease severity was assessed using LPSI (Lichen Planus Severity Index). Result: Serum levels of IL-23 and IL-17A were higher in cases (IL-23=414.0±510.7; IL-17A=139.4±192.1) than the controls (IL-23=22.9±33.5; IL-17A=2.90±2.06) and p value was <0.001, which was significant. These cytokines decline over time with a statistical significance. Male has a higher level (195.71±236.53) of serum IL-17A than female (72.84±86.38) with a p value=0.026). **Conclusions:** Serum levels of IL-23 and IL-17A were significantly elevated in patients with lichen planus and level of these cytokines decrease with increasing disease duration. IL-17A level in serum was higher in male than female indicating a possible sex specific way of IL-17A secretion. No relation of IL-17A and IL-23 with disease severity was observed.

Keywords: Lichen Planus, Association, IL-23, IL-17A

Introduction

Lichen planus is an autoimmune mucocutaneous disease that affects skin, mucous membranes, hair and nails. The incidence of lichen planus ranges from 0.14 to 1.27% of the general population. Two-third of the cases occur between the ages of 30-60 years. The disease can occur at any age though uncommon in children.[1]

The aetiology of lichen planus is unknown. Theories of infection including viral, bacterial, autoimmune, metabolic, psychosomatic and genetic causes have all had their proponents.[2]

In 2011, for the first time it was demonstrated that serum level of IL-17 in patient with lichen planus used to rise significantly and the issue that IL-17 may play a pivotal role in lichen planus pathogenesis was brought into the light.[3]

IL-17 renders to a family of six- members including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F.[4] and among them IL-17A is the prototype of the IL-17 family and often referred to as IL-17.[5]

Secretion of IL-17 through Th-17 cells is influenced by dendritic cell-derived IL-23.[6] A selectively pivotal role of the IL-23/IL-17 axis in the immune network of oral lichen planus lesions has been established.[7]

In cutaneous lichen planus IL-17 can induce associated pro inflammatory cytokines and antimicrobial peptide release.[8] For lichen planus the first two drugs in current treatment modalities are- steroid and acitretin which have potential side effects like HPA axis suppression, teratogenicity etc.[1] Despite treatment with various modalities lichen planus remains a therapeutic challenge

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and recurrence is common.[9]

Therapeutic targeting of T17 cells with agents that are antagonist to IL-23/IL-17 axis (secukinumab, ustekinumab, guselkumab) has been very effective in the clinical improvement of mucocutaneous lichen planus.[10]

This case control study was conducted to find out the association of serum IL-23/IL17 level with lichen planus and its severity by measuring serum IL-17 and IL-23 level in patients with lichen planus and healthy individuals which may help to add or modify the current treatment modalities or may lead to new immunomodulatory therapy that would be beneficial in lessening patients' sufferings.

Methods:

2.1. Sample size calculation

This was a Case-control study from August, 2021 to June, 2022 conducted in the Department of Dermatology & Venereology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh. Sample size was calculated to be 48 for each group using,

$n=((\sigma_1^2+\sigma_2^2)(z_{(1-\alpha/2)}+z_{(1-\beta)})^2)/(\mu_2-\mu_1)^2$

Here,

n =Sample size,

μ1= mean value of case

μ2= mean value of control

σ1= standard deviation for case

σ2= standard deviation for control

$z_{(1-\alpha/2)}$ = 1.96 for 5% level of significance and

$z_{(1-\beta)}$ = 0.842 (From Z table) at 80% power.

2.2. Inclusion criteria:

For case:

Patients with lichen planus diagnosed clinically and/or histopathologically

Lichen planus patients not undergoing any treatment for LP before the study

Age: ≥ 18 years

Both gender

Able to understand questions and communicate well.

For control:

Healthy attendants of patients, laboratory staff, postgraduate medical students, and general people of the same geographical area.

Age: ≥ 18 years

Both gender

2.3. Exclusion Criteria:

Patients suffering from chronic infection or inflammation (e.g. tuberculosis, SpA, rheumatoid arthritis), cardiovascular disease, hypertension, diabetes mellitus, allergic disease, malignancy, haematological diseases, pregnancy etc. Drug therapy may cause LP-like lesions such as NSAIDs, aspirin, ACE inhibitors, beta-blockers etc. or alter laboratory parameters (eg. corticosteroids). nflammatory skin (eg. Psoriasis, atopic dermatitis) or systemic disease (eg. Rheumatoid arthritis) or overt infections in patients and control.

2.4. Source of the sample:

Case: Patients with lichen planus attending the Department of Dermatology and Venereology BSMMU. They were diagnosed clinically by an expert dermatologist, with or without histopathological confirmation.

Control: Age and sex-matched healthy attendants of patients, laboratory staff, postgraduate students, and general people of the same geographical area.

2.5. Sampling method: Consecutive type of sampling.

2.6. Severity assessment: The severity of cutaneous lichen planus was assessed following Kaur (11), oral lichen planus following Malhotra (12) and nail lichen planus following Iorizzo (13).

2.7. Data collection technique: Data were collected in a predesigned data collection sheet and results obtained from laboratory methods were recorded.

2.8. Type of specimen: Blood samples from patient and control groups.

2.9. Sample collection: 3 ml blood was collected from each participant by venipuncture after proper disinfection, then centrifuged at 4000rpm for 5 minutes. Separated serum was stored at -25°C till analysis of cytokines. Collected data were checked, edited and analyzed with SPSS software package version-26.

Result

This case-control study was carried out with the aim of demonstrating the association of serum IL-23 and IL-17A levels with lichen planus and to find out the relation of these cytokines in disease severity. A total of 48 clinically and/or histopathologically confirmed patients of lichen planus and 48 healthy and age-sex-matched controls were enrolled in this study. Blood samples were analyzed by ELISA method to assess serum IL-17A and IL-23 levels in the Department of Microbiology and Immunology, BSMMU, Dhaka, Bangladesh.

Table I: Sociodemographic characteristics of the study populations (n=96)

Variables	Case (n=48)	Control (n=48)	p-value
Age group (years)			
<30	21(43.8%)	15(31.3%)	
31-40	13(27.1%)	22(45.8%)	
41-50	9(18.8%)	7(14.6%)	
>50	5(10.4%)	4(8.3%)	
Mean ± SD	35.4±11.6	35.5±9.79	1.000[ns]
Gender			
Male	26(54.2%)	29(60.4%)	0.536[ns]
Female	22(45.8%)	19(39.6%)	

Data were expressed as frequency and percentage and mean±SD Unpaired student t-test and Chi-square test were performed to compare the two groups ns = not significant The sociodemographic characteristics of study populations are shown in table-I. The mean age of respondents among cases (35.4±11.6) was slightly lower than the controls (35.5±9.79). Among study patients male candidates constitute 54.2% and female candidates constitute 45.8% and among controls 60.4% were male and 39.6% were female. To see the statistical significance of this difference, an Unpaired student t-test and Chi-square test was performed. Observed differences were not statistically significant. Other observed sociodemographic characteristics (marriage, occupation) also denote no statistical significance among cases and controls.

Table II: Distribution of the study patients (case) by location and severity of lichen planus (n=48)

Location and severity of Lichen planus	Frequency	Percentage (%)
Oral	14	29.2
Mild	2	14.3
Moderate	11	78.6
Severe	1	7.1
Nail	5	10.4
Mild	4	80.0
Moderate	0	0.0
Severe	1	20.0
Cutaneous	37	77.1
Mild/moderate	31	83.8
Severe	6	16.2

The percentage of distribution of study patients according to their site of involvement and clinical severity is shown in Table-II.

Total 37 patients had cutaneous involvement and 83.8% of them had mild/moderate severity according to LPSI (Lichen Planus Severity Index) of Kaur H et al 2019. Total 14 patients had oral lichen planus and most of them (78.6%) had moderate severity according to Malhotra AK et al,2007. Only 5 patients had nail involvement and all of them had mild disease except only one, who had severe nail lichen planus according to Iorizzo et al. 2020.

Table III: Comparison of serum IL-17A level and serum IL-23 level between case and control group (n=96)

Laboratory parameters	Case (n=48)	Control (n=48)	p-value
Serum IL-17A level (pg/ml) Mean± SD Median Range (min-max)	139.4±192.1 93.2 4.26-865.9	2.90±2.06 2.28 1.0-10.5	<0.001*
Serum IL-23 level (pg/ml) Mean± SD Median Range (min-max)	414.0±510.7 195.6 5.10-2221.6	22.9±33.5 12.6 7.10-192.0	<0.001*

p-value obtained by Mann-Whitney test, *significant

Table- shows the serum cytokine level of study populations. A significant difference was observed between cases and healthy controls, for IL-17A it was 139.4±192.1 vs 2.90±2.06, p <0.001 and for IL-23 it was 414±510.7 vs 22.9±33.5, p< 0.001.

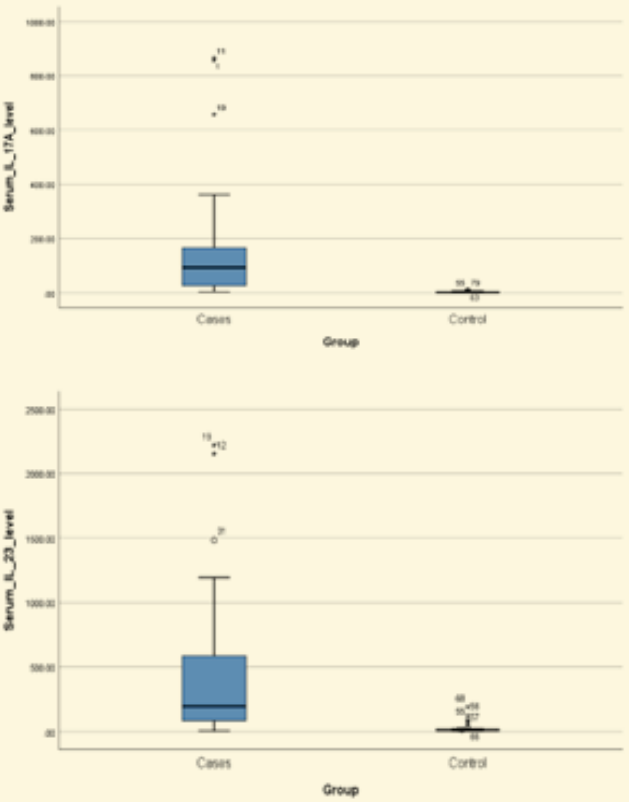

fig 1. Box plot showing the central tendency of serum IL-17A and serum IL-23 level

Here in Figure- the difference in the median value of serum cytokines (IL-17A and IL-23) between patients with lichen planus and healthy controls is shown. The dark line within each box indicates the median value. Fifty percent of the data lay inside the box. The line/ whisker extended from the box indicates the distribution of data. Indicators along this line with numbers indicates outliers (abnormally distributed data). Distribution is skewed to the longer whisker.

Table IV: Comparison of serum IL-17A level and serum IL-23A level among different demographic variables of case group (n=96)

Variables	N	Serum IL-17A Mean±SD	Serum IL-23A Mean±SD
Age group (years)[a]			
<30	21	137.46±194.78	321.34±329.45
31-40	13	153.58±172.64	425.84±576.48
41-50	9	175.06±259.83	654.64±683.04
>50	5	46.44±73.25	339.34±639.80
p-value		0.683[ns]	0.434 [ns]
Gender[b]			
Male	26	195.71±236.53	516.47±583.68
Female	22	72.84±86.38	292.92±387.11
p-value		0.026[s]	0.132 [ns]

p-value obtained by a ANOVA test and b Unpaired t-test, ssignificant, ns= not significant

Here in Table-IV serum level of cytokines (IL-17A and IL-23) among study patients were compared with different demographic variables. Age and occupation were compared with ANOVA test and no significance was found. Mean value of cytokines were compared with both gender and there was significant association of serum IL-17A level with gender of patients, p=0.026.

Table V: Comparison between disease severity and laboratory parameters (n=48)

Location and severity of Lichen planus	n	Serum IL-17A Mean±SD	Serum IL-23 Mean±SD
Oral			
Mild	2	98.1±101.4	343.2±433.2
Moderate	11	107.5±108.4	334.2±433.2
Severe	1	28.7	91.0
p-value		0.786[ns]	0.806 [ns]
Nail			
Mild	4	39.2±37.8	133.6±43.2
Severe	1	309.6	666.7
p-value		0.008*	0.002*
Cutaneous			
Mild/moderate	31	153.2±226.2	476.2±583
Severe	6	113.2±62.2	246.6±221.0
p-value		0.673 [ns]	0.353 [ns]

p-value obtained by Mann-Whitney test, *significant, ns=not significant

Here both IL-17A (p=0.008) and IL-23 (p=0.002) showed significant relation with disease severity in case of nail lichen planus. No significance was found with serum level of IL-17A and IL-23 level with severity in other variants of the disease.

Table VI: Distribution of the study patients (case) by disease duration (n=48)

Disease duration (months)	Frequency	Percentage (%)
< 24 months	36	75.0
≥24 months	12	25.0
Total	48	100.0
Mean ± SD	14.93±19.41	
Range (min-max)	(1.50 – 94.5) months	
Median	6.25	

Study patients were distributed according to disease duration in Table- . It shows that 75% of cases had the disease for < 24 months. The mean duration of the disease was 14.93±19.41.

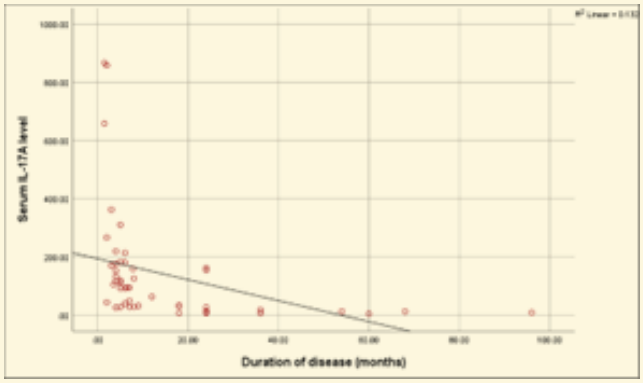

fig 2. Correlation of duration of disease with serum IL-17A level

p-value obtained by Pearson's correlation.
Pearson's correlation coefficient (r) test was done to see the relationship between disease duration and serum IL-17A level. Here, a negative (-) r value indicates an inverse correlation of IL-17A level with disease duration in lichen planus patients.

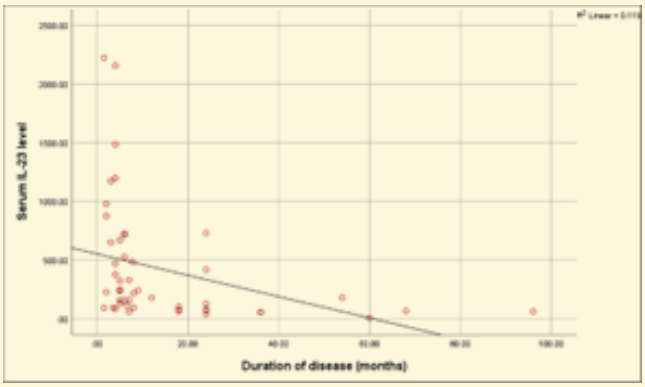

fig 3. Correlation of duration of disease with serum IL-23 level

p-value obtained by Pearson's correlation.
Pearson's correlation coefficient (r) test was done to see the relationship between disease duration and serum IL-23 level. Here negative (-) r value indicates an inverse correlation of IL-23 level with disease duration in lichen planus patients.

Table VII: Comparison of IL-17A and IL-23 between disease duration below 24 months and above 24 months (n=48)

	Disease duration				p-value
	<24 months (n=36)		>24 months (n=12)		
	Mean±SD	Median	Mean±SD	Median	
Serum IL-17A level	173.8±209.0	113.5	36.26±57.12	12.4	<0.001*
Serum IL-23 level	500.3±555.3	242.2	155.3±209	66.4	0.001*

p-value obtained by Mann-Whitney test, *significant, ns=not significant
Here in Table-VIII serum levels of IL-17A and IL-23 in between two groups of people (one having the disease for less than 24 months and another group for more than 24 months) are shown. For both cytokines, a significant decline in serum level over time was observed (for IL-17A, p<0.001 and for IL-23, p=0.001)

Discussion

Lichen planus is an autoinflammatory mucocutaneous disease that often follows a chronic course. Multifactorial aetiology and a complex interplay between innate and adaptive immune response have made the etiopathogenesis of the disease an unsolved mystery to date. A possible role of IL-17, the signature cytokine of Th17 cells and IL-23 as an important backbone material of effector Th17 cells have been suggested in many recent studies as an important immune-related pathogenetic mechanism behind the disease (7,14,15). Genetic predisposition has also been suggested as a responsible factor for lichen planus pathogenesis (16). Data focusing aetiopathogenesis of this geographic area is scarce to date.
This case-control study was designed to see the association of serum IL-23 and IL-17A levels with lichen planus and to find out the relation of these cytokines with disease severity. Forty-eight clinically and/or histopathologically confirmed patients of lichen planus and forty-eight healthy and age-sex-matched controls were included in this study. Clinical disease severity was assessed with various scales (11-13) according to the site of involvement in the Department of Dermatology and

Venereology, BSMMU, Dhaka, Bangladesh. Blood samples were analyzed by ELISA method to assess serum IL-17A and IL-23 levels in the Department of Microbiology and Immunology, BSMMU, Dhaka, Bangladesh.

In this study, the mean age of the patients was 35.4±11.6 years and the mean age of the controls was 35.5±9.79 years. This result is consistent with an epidemiological study done in India where the mean age of patients was 36.38 years (17). As the controls were selected according to matched age and sex, the value was not significant (=1.000), indicating that age will not affect other measuring variables. A major percentage of patients (70%) in this study aged below forty. Age is a primary risk factor for a number of chronic diseases. Type 2 diabetes mellitus, hypertension and other cardiovascular diseases are among the most serious ones (18). These diseases require regular consumption of some drugs (eg. Oral hypoglycemic drugs, thiazide diuretics, ACEIs) which may induce lichenoid eruption and may be indistinguishable from classic lichen planus (16). So the study population of this study was designed to avoid dilemmas regarding drug induction.

Slight male dominance (54.2%) was present among patients in comparison to females (45.8%). The oral disease was present among 14 patients and females constitute the majority (57.14%) though statistically insignificant (p=0.165). In lichen planus, no definite sex variation is seen but some studies claim the adults with oral presentation have female dominance whereas the childhood lichen planus has a male preponderance (19). As the exclusion criteria of this study exclude children (<18 years), male dominance in this group couldn't be assessed.

The concentrations of IL-17A and IL-23 in the serum of patients with lichen planus were significantly higher than those in the controls (IL-17A, p<0.001 and IL-23, p<0.001). IL-17A level was also found higher in the male gender. The high levels of IL-17A and IL-23 in the sera of patients of lichen planus have been reported in several studies but they reported no relation with sex. (3,15, 20).

All (21) also found the same observation in a comparative study between Psoriasis, lichen planus and atopic dermatitis. Serum levels of IL-17A and IL-23 were significantly higher among these three groups than the controls though he reported no relation between extent of disease, disease duration or gender. On the contrary, Mahmoud (14) reported a positive correlation between serum IL-17A level and extent of disease suggesting a possible relationship between serum IL-17A level and disease severity. He also reported no difference between serum levels of IL-17A between males and females.

On the point of sex-specific IL-17 levels, our study found a significant difference in serum IL-17A levels between males and females. In our study, the mean serum IL-17A level in males was 195.71±236.53 and in females, it was 72.84±86.38, p=0.026; which was significant. Studies in animal models have suggested that men are more prone to Th17 and Th2 dominance and women are thought to be more prone to Th1 dominance. TCR and CD28 signals coupled with male androgen have a direct effect in upregulating peroxisome proliferator-activated receptor α (PPARα) mRNAs in T cells of men and finally cause Th-17 cells to secret more IL-17A (22). Another recent study regarding the Th17 cellular effect in CNS autoimmunity showed that the male sex chromosomal component augments Th17 pathogenicity and promotes Th17 responses rather than androgens (23). Here, Zhang (22) claims that, though underlying influence may be different, there is male Th17 dominance in autoimmune disease which is consistent with our finding.

Regarding the relation of disease severity with serum cytokines levels, we found no relation except in nail lichen planus. Here nail lichen planus shows a significant relation between disease severity and serum level of cytokines, but the case number is too small (only five) to draw a conclusion. In his study, Mahmoud (14) measured severity in terms of the extent of body surface involvement expressed in percentage. There was no documentation of lesional description like, whether it was hyperpigmented, hypertrophic papule/ plaque, or only violaceous papule etc. On the other hand, this current study denotes different points for different morphology according to Kaur (11). On the other hand, considering these, it could be said that establishing the relation of disease severity with serum cytokines needs further exploration because lesional description along with different severity scaling for different lichen planus variants may make it difficult to interpret and align the results of different studies into an assimilated one.

The mean disease duration in this study was 14.93±19.41 months. & 75% of patients' disease duration is < 2 years (24 months). Cutaneous lichen planus spontaneously resolutes within 1-2 years, but oral lichen planus may take 5 years or more or

may adopt further chronic course. Lichen planopilaris causes permanent scarring alopecia (24).

In our study we found an inverse relation between IL-23 and IL-17A level with disease duration. Lu (7) mentioned positive correlations between the expressions of IL-23 and IL-17 at both protein and mRNA levels in the reticular oral lichen planus subgroup indicating upregulation of the IL-23/IL-17 axis in the early stage of disease. He found a lack of correlation between IL-23 and IL-17 in erosive lichen planus, which is the later stage of the disease. They mentioned persistent exposure to high levels of IL-23 might be a factor behind this and indicated potential regulator mechanisms other than IL-23/IL-17A might be responsible.

The plasticity of Th17 cells toward Th1 cells is linked to the prolonged exposure of Th17 cells to IL-23. There is a complex relationship between the Th1 and Th17 lineage's plasticity. The pathogenic Th17 cells engender the IL-17+IFNγ+ double-positive T cell subsets, termed as Th1 like Th17 or Th1/Th17. These cells secret both IFNγ and IL-17 and contribute to the pathogenesis of autoimmune disease but their production of IL-17 is much less than the Th17 cells before converting into Th1-like Th17 cells. Th-1 like Th-17 cells are also much resistant to Treg mediated suppression via IL-10. Thus autoimmunity is carried out (25).

The goal of this study was to demonstrate the association of serum IL-23 and IL-17A levels with lichen planus. Though the study sample was not sufficient enough to give the actual scenario of the total Bangladeshi population it will definitely give an overview about the association of these cytokines with different other variables in lichen planus. From the findings of this study, it is evident that serum IL-23 and IL-17A levels in patients with lichen planus are way too higher than the controls and there is a significant variation of cytokine levels in serum between males and females. No relation between generalized and localized disease with IL-23 and IL-17A levels has been found. The same goes for the relation between disease severity and serum cytokine levels. Regarding the course of the disease, this study found a significant diminish in serum cytokines in relation to disease progression, though no conclusion could be drawn about the obvious point of diminution of their serum level in the course of the disease, leaving scope for future studies.

Conclusion

This current study revealed serum IL-23 and IL-17A levels are significantly higher in patients with lichen planus. The serum level of IL-17A is much higher in male patients than the female. No relation between serum cytokine levels with disease severity. There lies an inverse relation between disease duration and serum cytokine levels in patients with lichen planus.

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