

Research Article

Elevated Serum Interleukin-23 Levels in Patients with Oral and Cutaneous Lichen Planus

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Received 1 March 2021; Accepted 3 June 2021; Published 12 July 2021

Academic Editor: Mirella Giovarelli

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Lichen planus is considered a chronic inflammatory disease which affects different sites, such as the skin, mucous membranes, hair, and nails. Based on the evidence, a complex cytokine network plays a crucial role in lichen planus pathogenesis. The study was aimed at assessing the serum IL-23 levels in the patients with cutaneous and oral lichen planus compared to healthy controls. *Method.* The study included 30 cutaneous lichen planus patients, 20 oral lichen planus patients, and 33 control subjects. Five milliliters of peripheral blood was obtained from each patient, and the serum was separated. IL-23 levels were determined using the ELISA kit, and the data were analyzed using the Mann–Whitney test. *Results.* IL-23 levels in the patient serum with oral lichen planus (P value ≤ 0.001) were significantly higher than in controls. Furthermore, there were significant differences in IL-23 serum levels in the patients with cutaneous lichen planus compared to the healthy controls (P value ≤ 0.001). Moreover, IL-23 serum levels were statistically different between patients with cutaneous lichen planus and patients with oral lichen planus (P value ≤ 0.001). Based on the mean concentration of interleukin-23, IL-23 levels were higher in the patients with oral lichen planus than in the patients with cutaneous lichen planus. *Conclusions.* Elevated serum IL-23 levels in the patients with oral lichen planus may indicate that IL-23 plays a crucial role in the pathogenesis of oral lichen planus. However, more research is needed with a larger sample size.

1. Introduction

Lichen planus (LP) is a chronic inflammatory disease which affects various parts of the body such as the skin, mucous membranes, hair, and nails. LP is common in 0.5–2% of the world population and has a variety of clinical subtypes based on the morphology of the lesions and the location of involvement [1, 2]. Oral lichen planus is more common and could affect the general population by 0.5% to 4% [3, 4]. OLP is characterized by a subepithelial infiltration of T lymphocytes and the degeneration of basal keratinocytes [5–7].

The dysregulation of inflammatory cytokines is the cause of various autoimmune diseases and allergies. IL-23 is a heterodimeric cytokine which belongs to the IL-12 family which contains a p40 and a unique p19 subunit. IL-23 is mainly produced by the dendritic cells and macrophages and

secreted by various cell types, such as activated dendritic cells, macrophages, and epithelia, and acts as an essential driving factor for the immune response [8]. IL-23 binds to CD4+T cells through the IL-23R and contributes to the maintenance and induction of TH17 to produce various cytokines, including IL-17A (IL-17), IL-17F, IL-22, IL-26, IFN- γ , CCL20, and TNF- α ; IL-17 activates the production of numerous inflammatory molecules such as cytokines, chemokines, defensins, and MMPs by activating the epithelia, endothelia, fibroblasts, chondrocytes, and osteoblasts [9, 10].

IL-23 is believed to be the main cytokine in the pathogenesis of inflammatory and autoimmune diseases [11, 12]. Furthermore, the evidence shows that the IL-23/IL-17 axis plays a critical role in the severity and chronic course of rheumatoid arthritis [13]. Besides, some previous research reported IL-23 involvement in the autoimmune diseases,

such as psoriasis and rheumatoid arthritis [14]. Immune-inflammatory factors and cytokines were thought to play critical roles in the development and immunopathogenesis of OLP [15]. Regarding the pathogenic role of cytokines in LP diseases, TNF- α , IFN γ , IL-10, IL-17, and IL-22 are to be involved in the pathogenesis of OLP [15]. IL-6, IL-10, INF- α , and TNF- α cytokines are also involved in the LP pathogenesis [16]. TNF- α production in saliva associated to OLP activity was also increased in the OLP patients [17]. The IL-17 serum level was higher in the patients with OLP compared to controls [18]. An increased serum concentration of IL-17 and a high expression in a skin lesion was reported in another study [19].

Few studies examined the IL-23 and its pathogenic role in LP. The present study was aimed at determining the IL-23 serum level in OLP and CLP patients compared to the controls.

2. Materials and Method

In this cross-sectional study, the entire sample comprised 50 patients: 30 patients with CLP and 20 patients with OLP, who were referred to the Oral Medicine Department and Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. 33 healthy control persons took part in this study.

Patients were matched with controls on age and gender. LP was confirmed both clinically and histopathologically. All selected participants did not use any systemic and topical drugs related to a leukemic reaction in the past three months and did not receive chemotherapy or radiation therapy in the past three months. Moreover, they had no inflammatory and autoimmune diseases or any cancer and were all non-smokers. All participants have signed the consent form. Ethical approval for this study was approved by Shiraz University of Medical Sciences, Shiraz, Iran.

2.1. Collection of Samples. Approximately 5 ml of peripheral blood was obtained from each subject. The samples were centrifuged to separate the serum and then stored at -20°C until further analysis.

2.2. Cytokine Assay. The IL-23 enzyme-linked immunosorbent assay (ELISA) kit (MyBioSource, San Diego, California, USA) was used to detect the IL-23 levels in the serum. Results were expressed in pg/ml for IL-23 in the serum.

2.3. Statistical Analysis. SPSS version 18 (IBM) was used for the statistical analysis, and the obtained results were expressed as the mean \pm standard deviation (SD). The Mann-Whitney test was performed to indicate the difference in IL-23 levels between patients and controls.

3. Results

The serum interleukin-23 levels were assessed in 30 CLP, 20 OLP, and 33 controls. The baseline characteristics of LP patients and controls are listed in Table 1.

The IL-23 concentration in the serum of patients with LP and healthy controls is shown in Table 2. As Table 3 shows,

the serum levels of IL-23 in OLP patients were significantly higher than those in the controls (P value ≤ 0.001). Serum IL-23 levels were also higher in the patients with CLP than in the control group (P value ≤ 0.001). The mean serum IL-23 level was also statistically higher in the patients with OLP than in the patients with CLP (P value ≤ 0.001) (Figure 1).

4. Discussion

Th17 and IL-23/IL-17 signaling pathways are implicated in many autoimmune diseases.

In this regard, previous research showed that the increased levels of IL-23 and IL-17 are linked to the pathogenesis of many autoimmune diseases, such as pediatric systemic lupus erythematosus [20], systemic lupus erythematosus, multiple sclerosis ankylosing spondylitis, Graves' disease, Crohn's disease [21] psoriasis, psoriasis arthritis [22, 23], chronic spontaneous urticarial [24], morphea [25], bullous pemphigoid [26], pemphigus vulgaris [27, 28], pemphigus foliaceus [29], and vitiligo [30].

Several studies have looked at the serum cytokine levels and saliva of patients with LP. However, concerning these controversial results, none of the cytokines studied suggests being the most useful indicator of the disease.

Xie et al. found a significantly elevated proportion of Th1 and Th17 cells in the peripheral blood and a significant increase in IL-17 serum levels in OLP patients, which might play an important role in the OLP pathogenesis [18].

In this regard, a published report showed elevated IL-17 and IL-23 serum levels in OLP patients with chronic periodontitis compared to healthy controls [31]. Significantly higher IL-23 serum levels were also observed in the patients with CLP and combined CLP and OLP patients than in healthy controls [32].

Our results showed an increased IL-23 level in the serum of CLP and OLP patients compared to controls. Besides, serum IL-23 levels in the OLP patients were significantly higher than serum IL-23 levels in the patients with CLP. Chen et al. found the same results for LP lesions. They showed increased expression of IL-22 and IL-23 in LP lesions and overexpression of IL-22 and IL-23 in OLP than in CLP [33, 34].

The role of the IL-23/IL-17 axis in the autoimmune and inflammatory diseases was commonly described. It appears that the IL-23/IL-17 axis also plays an important role in OLP pathogenesis.

In this regard, Lu et al. indicated the involvement of the IL-23/IL-17 axis in OLP pathogenesis. They suggested an interaction between T cells and the keratinocytes, in which the keratinocytes produce IL-23 in OLP lesions. Then, the IL-23 produced leads to the accumulation of Th17 cells and consequently to IL-17 overproduction in the local lesions of OLP. On the other hand, IL-17 induces the keratinocytes to produce various inflammatory mediators and form a complex immune network near OLP lesions [35].

Despite the advances in deciphering the Th17 transcription network, we still lack a clear understanding of the IL-23-

TABLE 1: Baseline characteristics of the study population with OLP, CLP, and controls.

Diagnosis	Cases (<i>n</i>)	Mean \pm SD age (years)	Age range (years)	Females (<i>n</i>)	Males (<i>n</i>)
Oral LP	20	51.31 \pm 13.68	28~84	16	4
Cutaneous LP	30	43.53 \pm 15.95	17~72	20	10
Control	33	48.68 \pm 9.95	17~65	26	7

TABLE 2: IL-23 concentration in patients with OLP and CLP and in controls.

ID/participants	IL-23 (pg/ml) OLP patients	IL-23 (pg/ml) CLP patients	IL-23 (pg/ml) Controls
1	93.38	56.08	84.51
2	67.09	56.08	48.28
3	58.37	60.21	19.03
4	72.14	60.66	42.31
5	81.55	58.37	145.15
6	148.11	81.55	45.98
7	56.37	55.82	41.39
8	73.05	59.23	45.38
9	120.99	50.11	45.52
10	116.56	58.37	53.78
11	97.33	56.08	42.31
12	82.04	74.89	51.95
13	82.03	50.11	92.40
14	68.42	50.57	45.52
15	55.16	89.44	54.70
16	65.25	92.89	38.68
17	69.84	51.49	41.39
18	67.55	57.91	53.78
19	61.58	52.41	61.58
20	83.03	68.92	48.28
21		60.21	45.98
22		76.72	47.82
23		48.28	50.72
24		68.01	41.39
25		62.96	68.46
26		57.45	51.03
27		63.88	54.70
28		60.66	51.95
29		57.45	56.54
30		48.74	56.54
31			56.08
32			53.78
33			68.92

dependent mechanisms which control the pathogenic Th17 differentiation process.

Therefore, STAT3-activated IL-23 is indispensable for the mediation of autoimmune pathology through the binding to pathogenic TH17 cells. The IL-23-activated Th17 cells promote chronic tissue inflammation, granuloma formation,

TABLE 3: Comparison of IL-23 levels in patients with OLP and CLP and control groups.

Variable	IL - 23 (pg/ml) \pm STD	Std. error	<i>n</i>	<i>P</i> value
Oral LP	80.99 \pm 24.07	5.38	20	≤ 0.001
Control	54.72 \pm 20.83	3.62	33	
Cutaneous LP	61.52 \pm 11.42	2.08	30	≤ 0.001
Control	54.72 \pm 20.83	3.62	33	
Cutaneous LP	61.52 \pm 11.42	2.08	30	≤ 0.001
Oral LP	80.99 \pm 24.07	5.38	20	

and autoimmunity. Accumulated data clearly show that TGF β , IL-6, and IL-1 β are essential elements that initiate Th17 cell development, while exposure to IL-23 is necessary for the differentiation and maturation of inflammatory Th17 cells. The ability of IL-23 to differentiate and stabilize pathogenic Th17 cells takes place through IL-23R expression upregulation, which in turn is STAT3-dependent. Moreover, TGF β 3 is induced by IL-23 and improves IL-23R expression.

Hence, IL-23 induces IFN γ expression in Th17 cells, and IFN γ +IL-17+ cells are highly pathogenic. Finally, it is important to mention that the skin resident cells, such as keratinocytes, fibroblasts, and endothelial cells, respond to IL-17. It is known that the STAT3-activated IL-23 is indispensable for mediating autoimmune pathology through the binding to pathogenic TH17 cells. The IL-23-activated Th17 cells promote chronic tissue inflammation, granuloma formation, and autoimmunity [36]. The accumulated data clearly shows that TGF β , IL-6, and IL-1 β are essential elements which initiate the development of Th17 cells, while exposure to IL-23 is necessary for the differentiation and maturation of inflammatory Th17 cells. The ability of IL-23 to differentiate and stabilize pathogenic Th17 cells is due to the upregulation of IL-23R expression which in turn is STAT3-dependent. Furthermore, TGF β 3 is induced by IL-23 and improves IL-23R expression. IL-23 induces the IFN γ expression in Th17 cells, and IFN γ +IL-17+ cells are highly pathogenic. Finally, the skin-resident cells such as keratinocytes, fibroblasts, and endothelial cells react to IL-17 [36].

A better understanding of the IL-23/IL-17 axis role in LP pathogenesis could help develop new therapeutic strategies for the prevention and management of LP in the future.

Thus, the drugs which target the IL-23/IL-17 axis may also result in the improved efficacy to treat the LP. In particular, when both IL-23 and IL-17 were blocked, remarkable results were obtained. The effectiveness of

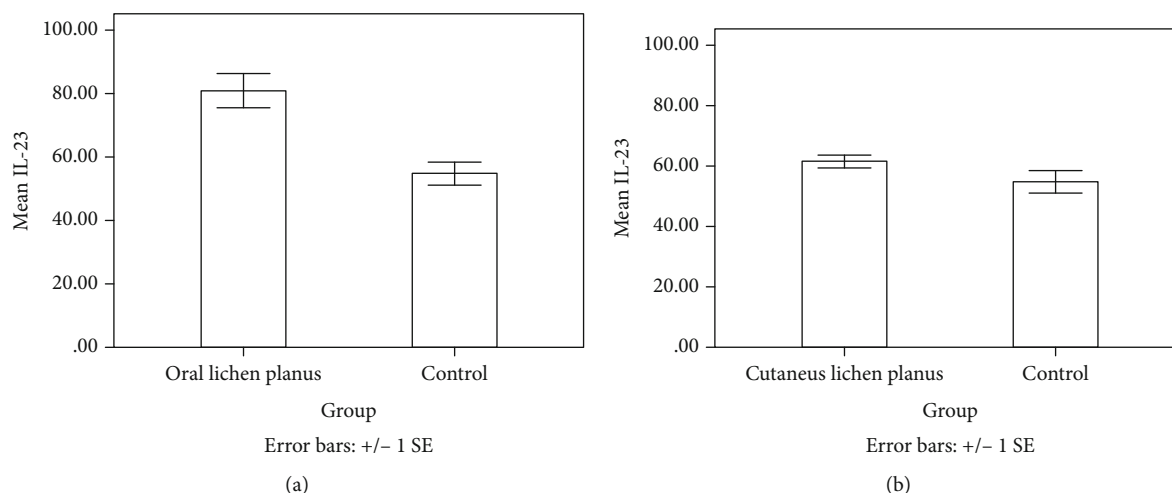


FIGURE 1: Comparison of the mean IL-23 serum levels between healthy controls and LP patients: (a) oral lichen planus (P value ≤ 0.001); (b) cutaneous lichen planus (P value ≤ 0.001).

such drugs to treat psoriasis and psoriatic arthritis was documented [22, 23].

Monoclonal antibodies against IL-23 alone or in combination with IL-12 were shown to be an effective therapy for psoriasis, multiple sclerosis, and systemic lupus erythematosus [37–43]. These antibodies may also be effective to treat the LP.

5. Conclusions

It appears that elevated serum IL-23 levels may be associated to its pathogenic role in LP, particularly OLP. However, more research with a larger sample size is required.

Data Availability

Data are found in the supplementary information files.

Ethical Approval

This study was approved by the local ethics committee of Shiraz Medical University, Shiraz, Iran (IR.SUMS.REC.1396.S685).

Consent

Before donating blood and publishing the data, informed consent was obtained from each participant.

Conflicts of Interest

The authors have no affiliation or involvement with any organization or organization with financial or nonfinancial interest in any of the topics or materials discussed in this manuscript.

Acknowledgments

This work was carried out as part of the dissertation of Dr. Hossein Mofidi performed as partial fulfillment for his dental

dissertation at the Faculty of Dentistry of the Medical University of Shiraz (SUMS). The authors would like to thank everyone involved in this project. This project was supported by a grant (Grant number: 1396-01-03-14576) from the Department of Dentistry at Shiraz University of Medical Sciences, Shiraz, Iran.

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