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Research Article

# TISSUE EXPRESSION OF INTERLEUKIN-17 SIGNIFICANTLY AND INDEPENDENTLY AFFECTS PRURITUS IN PSORIATIC PATIENTS: A CLINICOPATHOLOGICAL CORRELATION

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**ABSTRACT**

**Objective:** This study aimed at the evaluation of pruritus and its intensity and aggravating factors in psoriatic patients with the assessment of its relation to interleukin-17 (IL-17) expression in psoriatic lesions.

**Methods:** The study included 50 patients with psoriasis vulgaris. A questionnaire was used for the evaluation of pruritus and its effect on the quality of life. Severity of pruritus was assessed by the visual analog scale (VAS) while clinical severity of psoriasis was assessed using psoriasis area severity index (PASI) score. Tissue immunohistochemical expression of IL-17 was assessed in psoriatic lesions and in 20 normal skin biopsies included as control.

**Results:** Pruritus was encountered in 92% of psoriatic patients studied, 45.5% of them considered emotional stress as the main pruritus aggravating factor. Pruritus had influenced the daily activity and sleep in 91.3% of the studied patients. Mean VAS in studied cases was 5.70 ± 2.76. VAS grades were significantly associated with PASI scores and IL-17 tissue expression on univariate analysis. On multilogistic regression analysis, both IL-17 and PASI scores emerged as independent influencers of pruritus.

**Conclusion:** Pruritus is a common symptom that affects the quality of life in psoriatic patients. IL-17 is an independent aggravating factor of pruritus in those patients. To the best of our knowledge, this is the first study evaluating the tissue expression of IL-17 in relation to pruritus. Pruritus treatment should be one of our goals while managing the psoriatic patients and anti-IL-17 may play a pivotal role in this field.

**Keywords:** Interleukin-17, Pruritus, Psoriasis.

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## INTRODUCTION

Psoriasis is a common inflammatory skin disease affecting about 1–3% of the general population worldwide [1]. The pathogenesis of psoriasis is multifactorial including genetic, immunological, and environmental factors which contribute to the stimulation hyperproliferation and abnormal differentiation of keratinocytes [2]. Psoriasis is a T helper 1 (TH1)-mediated disease in which interferon gamma and tumor necrosis factor-α are the main cytokines involved in its pathogenesis [3]. Nowadays, the potential role of the TH17 cells and its related interleukin (IL) 23/IL-17 axis in psoriasis pathogenesis is well established [4].

Pruritus is an unpleasant sensation that drives the urge to scratch [5]. It has an impact on quality of life and it affects daily activity and sleep [6]. Pruritus is a major complaint in psoriatic patients but it is not well studied. Some studies reported that abnormal expression and secretion of neuropeptides including substance P, calcitonin gene-related peptide, somatostatin, beta-endorphin, and vasoactive intestinal peptide responsible for the itching sensation in psoriatic patients [7]. While, other studies focused on different mediators including histamine, IL-2, IL-31, E-selectin, and serotonin as possible inducers of itching sensation in psoriasis [8] even though the pathogenesis of psoriatic pruritus is still unclear.

IL-17 is highly expressed in psoriatic skin and is involved in a number of neuroimmune reactions [9]. In addition to immune cells such as TH 17, natural killer cells, monocytes, and neutrophils which are the main secretors of IL-17, it is also secreted by non-immune cells such as astrocytes and oligodendrocytes and microglia [10]. It was reported that IL-17 is involved in the induction of neuropathic pain [11]. In this work, we tried to study pruritus in Egyptian psoriatic patients, its correlation with tissue expression of IL-17 and finally the influence of this unpleasant symptom on the quality of life.

## METHODS

Fifty psoriatic patients were included in the study, inclusion criteria were as follows:

- Patients with classical picture of psoriasis vulgaris
- Patients did not receive treatment for at least 1 month.

Patients were selected from the Outpatient Clinic of the Dermatology and Venereology Department, Alexandria Main University Hospital, Egypt, during the period between June 2017 and June 2018.

A written informed consent was taken from all participants and the study was approved by the local Ethics Committee at Faculty of Medicine, University of Alexandria, Egypt.

The following groups were excluded from the study:

1. Pregnant and lactating females
2. Patients with any concomitant systemic disease which may induce itching, for example, hepatic, renal, hematological, and endocrinal diseases
3. Patients with any concomitant dermatological disease which may induce itching, for example, atopic dermatitis, scabies, and urticaria.

Clinical severity of psoriasis was assessed through calculation of psoriatic area and severity index (PASI) score [12].

### Evaluation of pruritus

A questionnaire form including five questions was used for the subjective assessment of pruritus by the patients:

- Question (1) what are the aggravating factors of pruritus?
- Question (2) for how long does the pruritus persist during the day?
- Question (3) is the pruritus getting better, worse, or unchanged from the time it started till the time of questionnaire?
- Question (4) does the pruritus affect sleep, social activities, and work?
- Question (5) what is the main site of pruritus?

The severity of pruritus was assessed by the visual analog scale (VAS). VAS is a graphic tool with a 100 mm horizontal line with the left end marked as "no symptom" and the right end marked as "worst imaginable symptom." The patient is asked to draw a vertical line to indicate the horizontal scale at a point that corresponded to the intensity of the symptom. The length from the left end to the vertical mark made by the patient is measured in millimeters and the severity was graded according to the following scale [13]:

- Grade zero: No pruritus
- Grade one: Mild pruritus (more than 0 and <3)
- Grade two: Moderate pruritus (from 3 to <7)
- Grade three: Severe pruritus (from 7 to 10).

**Skin biopsy**

Incisional biopsies were harvested from one of the psoriatic lesions in each patient. Twenty normal skin biopsies (taken from normal skin excised for mammoplasty procedures) were included in the study as control.

Five micron thick sections were cut from formalin-fixed, paraffin-embedded blocks of the skin biopsies. They were stained by H and E and examined by light microscopy for confirmation of the clinical diagnosis.

**Immunohistochemical staining**

Immunostaining was performed using an avidin-biotinylated immune peroxidase method. The primary antibody IL 17A (polyclonal, Cusabio CSB-PA06659) was used. The detection system and the primary antibody were provided by Lab Vision Corporation (Neo Markers, Fremont, USA).

The deparaffinized tissue sections were rehydrated in graded alcohols. The endogenous peroxidase was blocked using 0.3% hydrogen peroxide for 20 min. For antigen retrieval, sections were microwaved in a thermoresistant container (Coplin jar) containing citrate (10 mM, pH 6.0). The primary antibody was then applied at a concentration of 1:100. The reaction product was developed using diaminobenzidine tetrahydrochloride (DAB) mixture for 10 min. The DAB mixture was freshly prepared for each run (for each slide: 2 µl of DAB chromogen added to 100 µl of DAB substrate. Slides were counterstained with hematoxylin, dehydrated, and mounted.

**Evaluation of IL-17 expression**

After preparation of slides, they were examined by light microscope to confirm positive staining; then, 10 different non-overlapped high-power fields (HPFs) were examined in each slide for visual counting of lymphocytes expressing IL-17. The mean number of IL-17 expressing lymphocytes was calculated per HPF.

**Statistical analysis of the data**

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp.). Qualitative data were described using number and percent. The Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. Significance of the obtained results was judged at the 5% level.

- Correlation between quantitative variables was done using Spearman rank correlation test
- Monte Carlo significance test was used to test association between two qualitative variables in more than (2 × 2) table
- Kruskal–Wallis test was used to test the relationship between quantitative and qualitative variables.

## RESULTS

The age of the patients ranged from 19 to 65 years with a mean of 44.14 ± 13.16 years. Thirty cases were male (60%) and 20 were female (40%).

**PASI score**

PASI score in the studied cases ranged between 2 and 27 with mean PASI equal 10.26 ± 6.15 and median equal 8.2.

**Evaluation of pruritus in the studied cases**

Among the studied cases, 46 patients (92%) complained of pruritus and 4 patients (8%) had no pruritus.

The main aggravating factor that induced itching in our studied cases was emotional stress (45.5% of patients). Pruritus lasted for <6 h per day in 34.7% of patients. The course of itching was unchanged in 80.5% of cases.

The daily activities and sleep were affected by pruritus in 91.3% of patients and the most common sites affected by pruritus were lower legs followed by the head and scalp. The characteristic features of pruritus in our studied patients are summarized in Table 1.

**VAS**

The mean VAS in psoriatic patients of our study was 5.70 ± 2.76. VAS grade was 0 in 4 patients (8%), Grade 1 in 7 patients (14%), Grade 2 in 20 patients (40%), and Grade 3 in 19 patients (38 %).

**Results of IL-17 immunostaining**

Lymphocytes infiltrating the dermis in psoriatic lesions showed positive cytoplasmic staining for IL-17, the number of positively stained lymphocytes ranged between 25 and 556 with mean of 217.08 ± 124.88/HPF. It was significantly higher than that of the control group (mean per HPF was 9.80 ± 4.11) ($p<0.001$) (Fig. 1).

**Results of statistical analysis**

*Univariate analysis*

VAS significantly increased with increasing the clinical severity of the disease measured by PASI score (p=0.011, Kruskal–Wallis test), also

**Table 1: Subjective evaluation of pruritus in studied cases**

| Characteristics of pruritus in psoriatic cases | N= | (%) |
|---|---|---|
| Aggravating factors | | |
| Emotional stress | 21 | (45.5) |
| Sweating | 12 | (26) |
| Hot weather | 6 | (13) |
| Skin dryness | 2 | (4.5) |
| Heat | 2 | (4.5) |
| No aggravating factors | 3 | (6.5) |
| Duration per day | | |
| <6 h | 16 | (34.7) |
| 6–12 h/day | 13 | (28.3) |
| 12–18 h/day | 7 | (15.3) |
| All the day | 10 | (21.7) |
| Course | | |
| Unchanged | 37 | (80.5) |
| Improved | 3 | (6.5) |
| Worsened | 6 | (13) |
| Effect on activities and sleep | | |
| Never affects | 4 | (8.7) |
| Occasionally affects | 20 | (43.4) |
| Frequently affects | 14 | (30.5) |
| Always affects | 8 | (17.4) |
| Main site | | |
| Scalp and head | 16 | (34.7) |
| Face | 2 | (4.5) |
| Forearms | 3 | (6.5) |
| Abdomen | 1 | (2.1) |
| Back | 1 | (2.1) |
| Buttocks and thighs | 2 | (4.5) |
| Groin | 3 | (6.5) |
| Lower legs | 18 | (39.1) |

higher grades of VAS were associated significantly with higher IL-17 expression (p=0.040, Kruskal–Wallis test) (Table 2 and Fig. 2).

VAS was higher in males than that in females, however, the difference between the two groups was not statistically significant (p=0.508, Monte Carlo test), also no significant association could be detected between patients' age and VAS (p=0.515, Kruskal–Wallis test) (Table 2).

No significant correlation could be detected between IL-17 expression and PASI score in the studied cases (p=0.368, Chi-square/Spearman's test).

**Multivariate analysis**

Multilogistic regression analysis was applied to pick up the variables which independently affect pruritus. The model used included pruritus and the two significant variables in the univariate analysis, PASI score and IL-17 expression. The model was significant (p=0.000) and each of IL-17 expression and PASI score significantly emerged as independent variables affecting pruritus (p=0.008 and 0.000, respectively).

## DISCUSSION

Pruritus represents an important unpleasant complaint in psoriatic patients, in our study, the prevalence of pruritus among cases was 92%, this result is in concordance with other studies which concluded that pruritus is a frequent complaint among psoriatic patients, Peres *et al*. found that the prevalence of pruritus was 91.3% [14]. Furthermore, Stinco *et al*. studied 230 psoriatic patients and found that the prevalence of pruritus was 80% [15].

There are different aggravating factors for pruritus in psoriasis, in our study, emotional stress was the main aggravating factor, in agreement with our results, Dickison *et al*. found that stress was the main aggravating factor of pruritus in psoriatic patients [16]. Amatya *et a*l. found that skin dryness was the main aggravating factor of pruritus among their studied group [17]. On the other hand, Yosipovitch *et al*. found that ambient heat was the main aggravating factor of pruritus [18]. The difference in the climate and lifestyle between different countries in which the studies were done might be the reason for the difference in the main aggravating factors.

The majority of the cases in our study reported that pruritus had an impact on their daily activity and sleep. This highlights the importance of considering the alleviation of pruritus as an integral part of treatment of psoriatic patients. In agreement with our results, Stinco *et al*. [15] found that the majority of the patients in their study have reported that their quality of life decreased after the onset of psoriatic pruritus, in particular, a reduction in mood and sleep. Lebwohl *et al*. reported that itching sensation was described by patients as one of the most important factors contributing to perceived disease severity [19]. However, on the contrary, Peres *et al*. [14] did not find any association between pruritus that was measured by the Dermatology Life Quality Index score and the quality of life in the studied population. The perception of pruritus sensation is not only affected by its severity but also by many other factors related to the patients' personalities and their lifestyles.

The distribution of pruritus differed among different studies according to the sites of psoriatic plaques. In our study, the most common site was lower legs followed by the head and scalp. Yosipovitch *et al*. [18] reported that the areas most commonly involved were the back, legs, and arms. Amatya *et a*l. [17] reported that pruritus was localized to the lower legs, scalp, and arms. Those sites are the most accessible to the patients. Kim *et al*. suggested that increased epidermal nerve density in psoriatic scalp lesions may play a role in the development of pruritus in scalp psoriasis [20].

Using VAS, most patients in our study experienced moderate–to-severe pruritus. This is in accordance with the other studies in which the VAS among psoriatic patients ranged from 4 to 7 points [14,15,17,18,21].

In our study, there was statistically significant association between the VAS grades and PASI score, but the relation between the severity of psoriasis and itching is controversial among different studies, Stinco *et al*. [15], Szepietovski *et al*. [22], and Chang *et al*. [23] found a significant correlation between the severity of psoriasis and itching which is in agreement with our results, while Peres *et al*. [14], Nakamura *et al*. [24], and Yosipovitch *et al*. [18] did not find any correlation between the severity of psoriasis and itching. This highlights the possible contribution of other factors in the perception of pruritus sensation among psoriatic patients.

Although IL-17 expression was significantly higher in psoriatic lesions than that of the control group in our study, we did not find a significant association between IL-17 expression and severity of psoriasis measured by PASI score. Our results are in accordance with de Oliveira *et al*. [25]. On the contrary, Arican *et al*. [26], Budamakuntla *et al*. [27], and Yilmaz *et al*. [28] demonstrated significant correlation between IL-17 and PASI score, these contradictory results may be attributed to the difference in the clinical psoriatic subtypes included in the different studies and to the different methods employed for the assessment of IL-17 expression.

**Table 2: Relation between VAS and different parameters in psoriatic patients (n=60)**

| Patient's parameters | VAS | | | | | | | | p |
|---|---|---|---|---|---|---|---|---|---|
| | G0 (n=4) | | G1 (n=7) | | G2 (n=20) | | G3 (n=19) | | |
| | n | % | n | % | n | % | n | % | |
| Sex | | | | | | | | | |
| Male | 4 | 13.3 | 2 | 6.7 | 12 | 40 | 12 | 40 | 0.508 |
| Female | 0 | 0.0 | 5 | 25 | 8 | 40 | 7 | 35 | |
| Age (years) | | | | | | | | | |
| Min.–Max. | 21.0–58.0 | | 23.0–65.0 | | 28.0–65.0 | | 19.0–61.0 | | 0.515 |
| Mean±SD | 45.75±16.76 | | 49.71±15.55 | | 44.35±11.22 | | 41.35±13.83 | | |
| Median | 52.0 | | 52.0 | | 43.5 | | 40.0 | | |
| PASI | | | | | | | | | |
| Min.–Max. | 2.10–6.0 | | 2.30–21.0 | | 3.0–20.0 | | 2.0–27.0 | | 0.011* |
| Mean±SD | 4.32±1.62 | | 7.30±6.64 | | 9.53±4.40 | | 13.37±6.74 | | |
| Median | 4.60 | | 5.0 | | 8.0 | | 15.0 | | |
| IL-17 | | | | | | | | | |
| Min.–Max. | 25.0–221.0 | | 38.0–310.0 | | 75.0–459.0 | | 101.0–556.0 | | 0.040* |
| Mean±SD | 108.50±82.01 | | 148.71±104.22 | | 221.20±115.49 | | 260.79±130.99 | | |
| Median | 94.0 | | 144.0 | | 209.50 | | 220.0 | | |

VAS: Visual analog scale; PASI: Psoriatic Area and Severity Index; IL: interleukin; p: p value for association between VAS and different parameters, *Statistically significant at p≤0.05

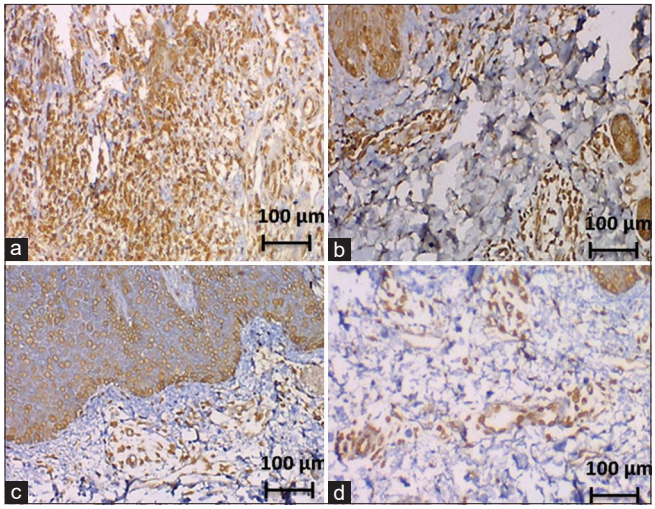


**Fig. 1: Cases of psoriasis vulgaris showing positive staining for IL-17 in inflammatory cells infiltrating the dermis (a) heavy staining; (b) moderate staining; and (c) mild staining (×200); (d) Normal skin showing scattered positively stained cells for IL-17 in the dermis. (Endothelial cells were positively stained for IL-17 and were considered as internal positive control) (×200)**

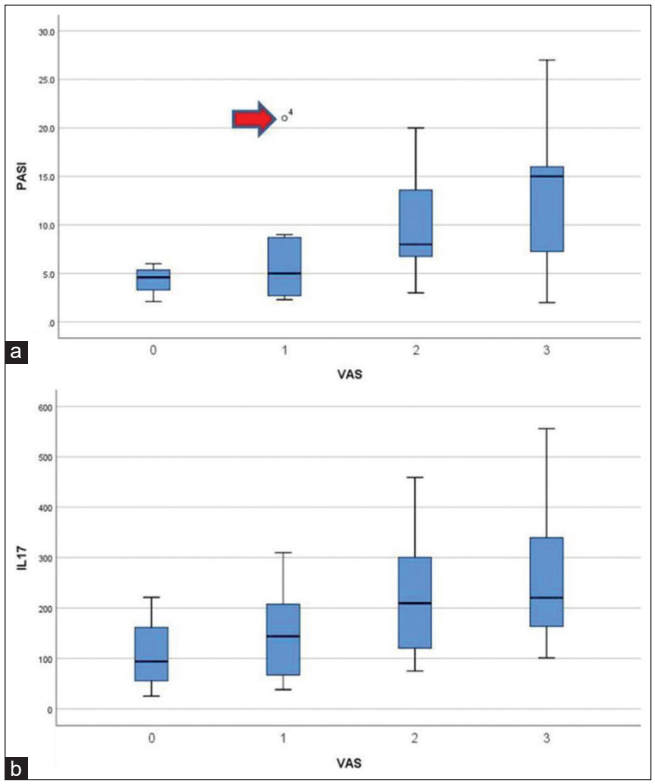


**Fig. 2: Box plot diagram showing (a) the distribution of the studied cases according to both visual analog scale and Psoriatic Area and Severity Index (PASI) score, one outlier is spotted (arrow), this case for a female patient aged 35 years with high PASI score 25 and mild pruritus (grade 1), in this female, IL-17 expression was as mild as pruritus (150/HPFs) irrelevant of the clinical severity; (b) the distribution of the studied cases according to both VAS and IL-17, no outliers were detected**

In spite of high prevalence of pruritus in psoriatic patients, its exact pathogenesis is still unclear. The important function of TH 17 cells and its related IL-23/IL-17 axis in psoriasis is now well accepted and studied [4]. In our study, we found a significant correlation between the tissue expression of IL-17 and pruritus which highlights the importance of IL-17 as an itching mediator. In agreement with our results, Blauvelt *et al*. found that Secukinumab, a fully human immunoglobulin G1 monoclonal antibody that neutralizes IL-17A, can reduce psoriatic itching [29]. IL-17 has direct effects on neurons and can also affect neural function indirectly through immune cells, it also acts at the level of dorsal root ganglia and the spinal cord where it may modulate the perception of itching [30]. On the contrary of our results, Czarnecka-Operacz *et al*. did not observe any significant relationship between IL-17 and pruritus in psoriatic patients [31]. We suggested that the contradictory results may be explained in fact that tissue expression of IL-17 is more representative of its pruritogenic effect than its serum level.

The multilogistic regression analysis held in our study was aiming at evaluating the precise relation between IL-17 and pruritus. A significant model including IL17 and clinical severity PASI as aggravating factors of pruritus was used. Both IL-17 and PASI emerged as independent influencers of pruritus. This means that IL-17 regardless of the clinical severity can aggravate pruritus in psoriatic patients. This could explain the rare cases seen in clinical settings as well as in our study of patients suffering from severe pruritus early in psoriasis and those with advanced disease but with mild pruritus. This result also explains the insignificant correlation between IL-17 and PASI encountered in our study.

In the Box plot diagram used in our study, representing the distribution of cases according to both VAS and PASI score variables, one outlier was spotted, this was for a female patient aged 35 years with high PASI score 25 and mild pruritus (Grade 1), in this female, IL-17 expression was as mild as pruritus (150/HPFs) irrelevant of the clinical severity.

## CONCLUSION

Pruritus is a frequent complaint among psoriatic patients which affects the quality of life. It is aggravated by emotional stress and seasonal variations. The severity of pruritus among psoriatic patients increases with increasing the clinical severity of the disease. IL-17 emerged as a significant and independent aggravating factor of pruritus in psoriatic patients. The pruritus treatment should be one of our goals while managing psoriatic patients and anti-IL-17 may play a pivotal role in this field.

## AUTHORS' CONTRIBUTIONS

Ossama Hussein Roshdy, Ahmed Abdel-Bary: Conception and planning of the study; collection of the data, review of the literature, and editing of the manuscript.

Samar Nabil El-Achy: Collection of the data and editing of the manuscript.

Asmaa Abdel Wahab: Collection of the data and participation in the design of the study.

## CONFLICTS OF INTEREST

No conflicts of interest.

## AUTHORS' FUNDING

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N.B: A written informed consent was taken from all participants and the study was approved by the local Ethics Committee at Faculty of Medicine, University of Alexandria, Egypt.

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