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The role of interleukin-22 in pityriasis rosea

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Summary

Background. Pityriasis rosea (PR) is an exanthematous disease related to reactivation of human herpes virus (HHV) types 6 and 7. The pathogenesis and cytokine profile of PR are still poorly understood.There is a large amount of evidence indicating a viral aetiology for PR.

Aim. To measure the serum level of interleukin (IL)-22, a cytokine expressed by T helper (Th)17 cells in patients with PR to explore the possible association of IL-22 with the pathogenesis of the disease.

Methods. This case–control study enrolled 25 patients with PR (mean ± SD age 20 ± 12 years) and a control group of 25 apparently healthy individuals (mean age 18 ± 12.1 years). Blood samples were collected from both patients and controls to measure serum IL-22. Scoring of PR was performed using the Pityriasis Rosea Severity Score (PRSS).

Results. There was a statistically significant difference in IL-22 serum level between the patient and control groups. The IL-22 serum level increased with increase in disease severity (PRSS), extent and duration.

Conclusion. Through its proinflammatory cytokines, IL-22 plays a role in the inflammatory process of PR.

Introduction

Pityriasis rosea (PR) is a common, self-limiting, exanthematous disease seen in both children and adults. Classically, PR begins as an erythematous, scaly patch on the trunk known as the 'herald patch'. PR lasts for 6–8 weeks on average.[1] The definite cause of PR is unknown, but it has been hypothesized to be due to an infectious agent because of 'outbreaks' of PR among certain groups. There is increasing evidence implicating endogenous reactivation of human herpes virus (HHV)-6 and/or -7 as the cause of PR.[2–4] It is thought that the skin lesions of PR are not the result of direct infection of skin cells by HHV, but rather occur as a reactive response to the systemic replication of the virus, alone or through interaction with other viruses.[5]

Immunohistological studies have shown the presence of T cells and Langerhans cells (LCs) within the inflammatory dermal infiltrate of PR lesions, suggesting a role for cell-mediated immunity in the disease.[6]

Previously, fractalkine (a large cytokine protein of 373 amino acid) was demonstrated to be increased in patients with PR. Fractalkine is expressed on natural killer cells, monocytes, CD8 and CD4 T cells, and activates diverse intracellular signalling pathways.[7] Interleukin (IL)-22, a cytokine expressed by T helper (Th)17 cells, is increased in the sera of patients with active PR. The involvement of these chemokines, which promote the antimicrobial defence system and protect against damage, suggests an active immunological response in PR.[4,8] However, the pathogenesis of PR and its cytokine profile are still poorly understood.

The aim of this study was to measure the level of IL-22 in the serum of patients with PR in comparison with healthy controls (HCs) to explore the possible association of IL-22 with the pathogenesis of the disease.

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Methods

The study was approved by the Institutional Review Board of Zagazig University Hospitals, and performed in accordance with the principles of the Declaration of Helsinki. Informed written consent was obtained from all participants (or their parents, where appropriate).

Study design

This case–control study was carried out in the Dermatology, Venereology and Andrology Department at Zagazig University Hospitals during the period from June 2012 to June 2013. The study had two groups: a patient group and an HC group.

Participants

The patient comprised 25 patients with PR (6 male, 19 female; mean ± SD age 20 ± 12 years, range 4–48). The inclusion criterion was presence of the classic clinical finding of PR, and the diagnosis was made clinically. Patient had different disease stages and extents. Exclusion criteria were use of cytostatic or immunosuppressive drugs within 3 months proior to study entry, or presence of a rash (atypical for PR), infectious disease, or any local or systemic disease most probably associated with increased serum level of IL-22 (e.g. psoriasis).

The HC group comprised 25 apparently healthy individuals (12 male, 13 female; mean ± SD age 18.5 ± 12.1 years, range 3–48.

Assessments

Scoring of PR was performed using the Pityriasis Rosea Severity Score (PRSS) (Table 1).[9] The pruritic symptoms were also assessed with a 0–3 scale [0 = absence of pruritus; 1 = mild pruritus (if it occurred only intermittently and it did not interfere with work or rest), 2 = moderate pruritus (if it was present for much of the day, but at a more tolerable level) and 3 = severe pruritus (if it interfered with daytime activities or sleep)].[10] Evaluation of the psychosocial impact of disease was performed using the Dermatology Life Quality Index (DLQI).[11].

Evaluation of serum interleukin-22 level using ELISA

Blood samples (3 mL) were collected from all participants into serum separator tubes and allowed to clot for 30 min before centrifugation for 15 min at 1000 ***g***. Serum was separated and stored at −80 °C until analysed, avoiding frequent freeze/thaw cycles. IL-22 was measured using a commercial ELISA kit (Human IL-22 Quantikine ELISA Kit; R&D Systems Inc, Minneapolis, MN, USA). The reference range was from undetectable levels to 53.3 pg/mL. Blood samples were collected from both patients and controls, and then serum was separated and kept at −80 °C at the laboratory until the measurement of IL-22 using commercial ELISA kit.

Table 1 Pityriasis rosea severity score.[9]

Score	No. of lesions (N)	Erythema (E)	Infiltration (I)	Scaling (S)
0	0	Absence	Absence	Absence
1	1–9	Mild (slightly pink)	Mild (perceptible infiltration)	Mild (perceptible scaling)
2	10–19	Moderate	Moderate	Moderate
3	≥ 20	Severe (intense)	Severe (thick papule or plaque)	Severe (thick)

Statistical design

Data were checked, entered and analysed using EPI-INFO 6 for data processing and statistic. Student *t*-test and χ^2 test were used as appropriate. $P < 0.05$ was considered statistically significant.

Results

The demographic and clinical data of participants are presented in Table 2.

There was a statistically significant difference in IL-22 serum level between the two groups ($P \leq 0.001$) (Table 3). There was no statistically significant difference in IL-22 level between the sexes for both the patient and control groups ($P > 0.05$).

For patients, there was no statistically significant difference ($P > 0.05$) in IL-22 level between different age groups (< 20 or > 20 years) (Table 4). There was a statistically significant association between IL-22 level and stress ($P \leq 0.04$) (Fig. 1a, Table 4), and between IL-22 level and prodromal symptoms ($P = 0.01$) (Table 5).

There was a highly significant association between IL-22 level and disease extent score of 3 ($P = 0.001$) (Fig. 1b, Table 5), and between IL-22 level and pruritus scale (Fig. 1c). There was a positive correlation between IL-22 level, DLQI and PRSS (linear

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Table 2 Demographics of participants.

Parameter	Patients (n = 25)	Controls (n = 25)
Age, years		
Mean ± SD	20 ± 12	18 ± 12.1
Range	4–48	3–48
Sex, n (%)		
Male	6 (24.00)	12 (48.00)
Female	19 (76.00)	13 (52.00)
Personal history of PR		
Positive	25 (100.00)	0 (0)
Negative	0 (0)	25 (100.00)
Family history of PR		
Positive	0 (0)	0 (0)
Negative	25 (100.00)	25 (100.00)
Duration of PR, days		
Mean ± SD	16.6 ± 16.0	–
Range	4–60	–
Associated conditions, n (%)		
Pregnancy		
Positive	1 (4.00)	–
Negative	24 (96)	–
Stress		
Positive	16 (64)	–
Negative	9 (36)	–
Type of PR		
Classic	24 (96)	–
Inverted	1 (4)	–
Disease extent		
1	4 (16)	–
2	9 (36)	–
3	12 (48)	
Pruritus scale		
0	6 (24)	–
1	12 (48)	–
2	7 (28)	–
DLQI		
Mean ± SD	7.8 ± 4.5	–
Range	1–18	–
Interleukin-22 level		
Mean ± SD	339 ± 221	–
Range	56–800	–
PRSS		
Mean ± SD	21.9 ± 9.7	–
Range	4–39	–

DLQI, Dermatology Life Quality Index; PRSS, Pityriasis Rosea Severity Scale.

Table 3 Level of IL-22 in the groups.

IL-22	Patients (n = 25)	Controls (n = 25)
Mean ± SD	339 ± 221.1	9.2 ± 7.2
Range	56–800	0.5–31
Median	280	4.4
Mann–Whitney U-test	36.8	
P	< 0.001*	< 0.001*

*IL, interleukin. Highly significant.

Table 4 Association between IL-22 and age, stress and prodromal symptoms in patients.

		IL-22			
Parameter	n	Mean ± SD	Range	t-test	P
Age, years					
< 20	13	391.1 ± 226.9	70–800	1.24	0.22*
> 20	12	282.5 ± 209.4	56–750		
Stress					
Positive	16	406.9 ± 228.4	56–800	2.2	0.04†
Negative	9	218.2 ± 152.6	60–520		
Prodromal symptoms					
Positive	16	259.1 ± 157.4	56–600	2.7	0.01†
Negative	9	481.1 ± 254.5	70–800		

IL, interleukin. *Nonsignificant; †significant.

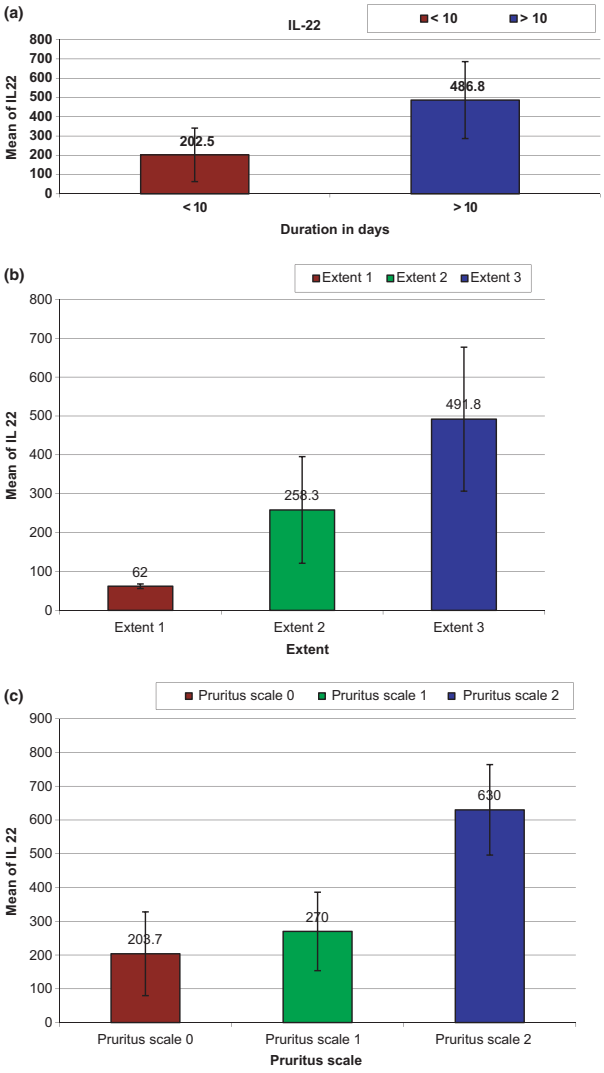

Figure 1 Association between mean interleukin (IL)-22 level and (a) disease duration, (b) disease extent and (c) pruritus score.

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Table 5 Association between interleukin-22 and disease extent.

		IL-22			
	n	Mean ± SD	Range	*F*-test	*P*
Disease extent (score)					
1	4	62 ± 5.9	56–70		< 0.05
2	9	258.3 ± 137.2	130–600		< 0.05
3	12	491.8 ± 185.2	222–800	13.4	< 0.001*

*Highly significant.

distribution), indicating that evaluation of the psychological impact of the disease on patient quality of life showed a significant increase in line with increases in IL-22 level and PRSS (Fig. 2, Table 6).

Discussion

The relation between PR and HHV-6/-7 has been well established,[12–14] but the elusive pathogenesis of the disease remains a subject of interest. It has been shown previously that HHV-6/-7 are active during the early stage of PR, suggesting that these viruses might play an aetiological role in this disease. In addition, it has been shown that plasma load of HHV-6/-7, which are direct markers of viral replication, is associated with the development of systemic symptoms and with a significant reduction of the humoral neutralizing response against HHV-6/-7, further suggesting that PR may be a result of the endogenous reactivation of HHV-6/-7 infection.[15]

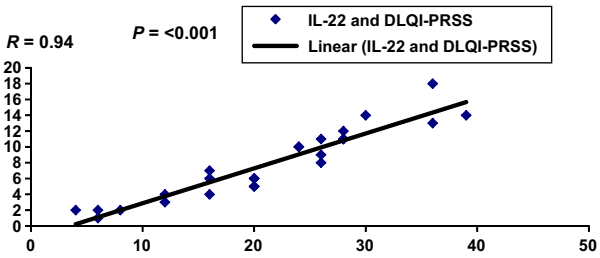

Figure 2 Correlation between DLQI (Dermatology Life Quality Index), PRSS (Pityriasis Rosea Severity Scale) and interleukin (IL)-22 level.

Table 6 Correlation between IL-22 and other parameters.

	*r**	*P*
DLQI	0.94	< 0.001†
PRSS	0.94	< 0.001†

DLQI, Dermatology Life Quality Index; IL, interleukin; PRSS, Pityriasis Rosea Severity Scale. *Correlation coefficient; †highly significant.

In addition, an increase in LCs and presence of activated T cells (with an increased CD4+ vs. CD8+ T ratio) have been reported in the dermal infiltrate of PR lesions, confirming that the interaction between Th cells, LCs, and inflammatory dendritic dermal and epidermal cells may represent a pathogenetic mechanism in a virus-triggered microenvironment in PR.[16]

Studies of the cytokine profile in PR are necessary to decipher the role of the activated T cells and to further characterize the Th1 and Th2 profile in PR. Recent studies have challenged the Th1/Th2 paradigm by discovering several Th subsets with specific differentiation programmes and functions, including Th17 cells, regulatory T cells, and follicular Th cells. Th17 cells are characterized by production of IL-17, IL-21, IL-22, and other cytokines.

IL-21, in addition to stimulating the proliferation and differentiation of activated leucocytes, acts by an autocrine mechanism on Th17 cells, stimulating in turn the production of IL-17 and other cytokines.[17] IL-17 is upregulated in the serum of patients with PR, and its key role in host defence against certain pathogens is well known. In addition, IL-17 and IL-22 are cytokines produced mainly by Th17 cells.[18] The significant increase in both cytokines supports the involvement of HHV-6/-7 in the PR pathogenesis.[19]

IL-22 has been found to have a dual nature of action: protective vs. inflammatory. The functional outcome of this cytokine depends on the inflammatory context, which includes, but is not limited to, the duration and amount of IL-22 present, the overall cytokine milieu and the tissues involved.[20] It was found to be protective during hepatitis through activation of antiapoptotic and prosurvival pathways.[21] By contrast, it was strongly expressed in several chronic inflammatory conditions, including rheumatoid arthritis, atopic dermatitis and psoriasis. In psoriasis, IL-22 upregulates the expression of S100A7-psoriasin, S100A8, S100A9, platelet-derived growth factor, CXCL5 and β-defensins; these proteins are known to have proinflammatory, chemotactic and/or antimicrobial properties, and they also produce hyperplasia in the skin.[17,22] Therefore, the notion that IL-22 may functions in the same way in PR, which is a papulosqaumous disease like psoriasis, is of interest. The aim of this study was to investigate the possible role of IL-22 in PR, and to correlate its level with patient age and sex, personal and family medical history, disease duration and extent, pruritus severity, prodromal symptoms, PRSS, and DLQI. To our knowledge, the role of IL-22 in PR has rarely been studied, except for the work of Gangemi *et al.*,[8] who studied its level and role in PR in

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relation to patient age and sex. In the present study, IL-22 level was significantly higher in patients with PR than in HCs. This may be due to the proinflammatory nature of this cytokine, which is in line with the hypothesis of a viral infection pathogenesis. Our results were in accordance with the results reported by Gangemi *et al.*[8] There was no significant relation between IL-22 level and either age or sex; these results are in accordance with those reported by Gangemi *et al.*,[8] who also found no significant relation between IL-22 level and sex in normal subjects.

In the current study, there was a significant relation between serum level of IL-22 and disease, indicating that the inflammatory process is still ongoing and the immune system is producing mediators to try to overcome the viral infection. Gangemi *et al.*[8] did not study this finding as their samples were taken at an early stage of the disease.

In relation to disease extent, there was a positive relation between IL-22 serum level and disease extent score.[3] It is likely that IL-22 level and its proinflammatory cytokines are increased in an attempt to combat the spreading viral infection, thus producing the resulting inflammatory skin condition.

There was also a significant relation between serum IL-22 level and increased pruritus score. This is most likely due to the higher levels of proinflammatory cytokines and the continuous inflammatory process mediated by the higher IL-22 concentration.

Finally, there was a positive correlation between DLQI, PRSS, duration and IL-22 level (linear distribution); IL-22 level increased as DLQI, PRSS and duration increased. This is in contrast to the results of Antonio and Henry,[23] who reported that DLQI had no relation to rash severity. The positive correlation between PRSS and DLQI (linear distribution) may be due to the higher levels of proinflammatory cytokines and the continuous inflammatory process mediated by the higher IL-22 concentration and higher disease severity.

A female predominance was found in this study, which is in accordance with the results of Chuh *et al.*,[24] who found a slight female predilection, with an overall male to female ratio of 1–1.43.

This study of IL-22 enlarges the list of cytokines involved in the pathogenesis of PR. Another recent study[18] investigated the cytokine and chemokine network in PR, providing evidence that circulating IL-17, interferon, vascular endothelial growth factor and CXCL10 are increased in patients with PR, and speculated on the putative role of these key cytokines in PR pathogenesis.

There are some limitations to this study. We did not investigate other IL-22-associated parameters such as natural killer (NK) cells, nor did we carry out any qualitative or quantitative investigations into the function of NK cells in patients with PR, thus more studies on the cytokine network in PR are warranted.

Conclusion

The inflammatory process mediated by IL-22 is aimed at combating the spreading virus and this explains the self-limiting behaviour of PR. This process is also responsible for the appearance of PR lesions (hyperkeratosis, acanthosis and nonspecific dermal inflammatory infiltrate). The increased IL-22 serum level and its correlation with disease severity may prove to be a future therapeutic target; however, the cost–benefit relationship limits the usage of such expensive treatments.

What's already known about this topic?

- Previous studies have shown that cytokine levels are increased in PR.
- It has also been shown that IL-22 is necessary for development of dermal inflammation in psoriasis, which is a papulosquamous disorder similar to PR.

What does this study add?

- We found IL-22 to have a role in the inflammatory process of PR through its proinflammatory cytokines.
- Our results indirectly support the viral infection hypothesis for PR.

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