Assessment of the Quality of Life, Prevalence of Depression, and the Level of Interleukin 6 in Patients with Pemphigus Vulgaris

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ABSTRACT Pemphigus vulgaris (PV) is a life-threatening, autoimmune blistering disease affecting the skin and mucous membranes, exerting a detrimental effect on the quality of life (QOL). Our aim was to evaluate the psychological status and QOL of patients with PV and investigate Interleukin-6 (IL-6) as a possible contributor to the pathogenesis of pemphigus and associated depression. The study included 22 patients with PV, 21 patients with depression, and 20 normal controls. All the 63 participants were subjected to assessment of their QOL, psychiatric profile, as well as estimation of serum level of IL-6. All (100%) of the included patients with PV had a negative effect on their QOL, which was significant compared with controls (P<0.001). Among patients with PV, 13 patients (59.1%) had depression. IL-6 was non-significantly elevated in the pemphigus group when compared with the controls (P=0.057). QOL was significantly worse in the depressed pemphigus subgroup compared with the non-depressed pemphigus subgroup (P=0.006 and <0.001) respectively. However, IL-6 was non-significantly elevated in the depressed pemphigus subgroup compared with the non-depressed pemphigus subgroup (P=0.095). A marked deterioration in the QOL was observed in patients with pemphigus. More than 50%, but not all, of patients with pemphigus had depression. IL-6 was non-significantly elevated in patients with pemphigus.

KEY WORDS: pemphigus, quality of life, immunobullous disease

INTRODUCTION

Pemphigus vulgaris (PV) is a chronic disabling disorder, characterized by painful oral erosions and flaccid skin blisters. It occurs due to IgG autoantibodies against desmoglein 3 (Dsg3), leading to acantholysis of keratinocytes and blister formation (1). Presentation by painful oral and cutaneous erosions, difficulty in eating, in addition to the disfiguring nature of the disease and avoidance of social interaction, all exert a negative effect on the patients quality of life (QOL). Furthermore, the need for long-term hospitalization, the financial burden, and side-effects of treatment can ultimately lead to different psychiatric disorders

including profound depression associated with suicidal ideation (2).

Previous studies have investigated the role of different inflammatory cytokines such as interleukin (IL)-1, IL-2, IL-6, and TNF-alpha in PV pathogenesis (3). The same cytokines were suggested to precede depressive symptoms, providing support for a pathway from inflammation to depression. IL-6 was found to be elevated in sera and blister fluid obtained from patients with PV and it was suggested it plays a role in acantholysis. During remission with immunosuppressive treatment, a decreased level of IL-6 was detected in PV (4). Adults with depression similarly showed raised inflammatory markers, including IL-6 (5).

This study aimed at evaluating the psychological status and the QOL among patients with PV, in addition to investigating IL-6 as a possible contributor to the pathogenesis of pemphigus and the associated depression.

PATIENTS AND METHODS

This study was conducted at the Dermatology Outpatient Clinic and has been approved by the Dermatology Research Ethical Committee (Derma REC) with informed consent signed by all participants.

Twenty-two patients with PV were recruited; diagnosis was based on both clinical and histopathological examination. Inclusion criteria included: fresh cases of PV (not previously treated) and patients in exacerbation being off any treatment for at least 2 weeks. Patients with diabetes mellitus, neurological disease, autoimmune diseases, or any malignancies were excluded as there is growing evidence that IL-6 play a role in such diseases (6,7).

For all patients, a full detailed history was taken and complete general examination was performed with emphasis on the general condition and excluding manifestations of internal malignancy. Lymphadenopathy, hepatosplenomegaly, jaundice, and pelvi-abdominal masses were ruled out.

Dermatological examination was performed at the time of presentation by two fixed investigators to determine the type of PV as mucosal (MPV) or mucocutaneous (MCPV). The mucosal type was defined as that with limited skin involvement (<6 erosions or blisters and each <5 cm in diameter), whereas the mucocutaneous type was defined as that with extensive skin involvement (>6 erosions or blisters, >5 cm in diameter) (8). The severity of the included cases was calculated using the pemphigus area and activity score (PAAS) (9). A final grading of being free, mild, moderate, or severe was calculated accordingly (Table 1).

Twenty-one patients with depression without a known autoimmune or dermatological disease were recruited from the Psychiatry Outpatient Clinic, Kasr

Table 1. Pemphigus area and activity score (PAAS) for cutaneous and mucus membrane lesions (9)

Clinical markers (Body lesions)	Clinical scores						
	0	1	2	3	4	5	6
A: Activity – No. of new blisters/day – Peripheral extension of existing blisters – Nikolsky's sign B: Area (%)	0 Nil -ve Nil	1-5 Mild Perilesional 0-15	6-10 Moderate Distant 16-30	11-20 Extensive - 31-50	>20 - - 51-70	- - - 71-90	- - - >90
Mucous membranes lesions	Clinical scores						
	0	1		2		3	
Area Severity	Nil Nil	1 site Mild		2 sites Moderate		>2 sites Severe	

Head score (H) = [(a + b + c) × score of area] ×0.1.
Trunk score (T) = [(a + b + c) × sore of area] ×0.3.
Upper limbs score (UL) = [(a + b + c) × score of area] ×0.2.
Lower limbs core (LL) = [(a + b + c) × score of area] ×0.4.
Total cutaneous score + H + T + UL + LL.
*Grade; free: 0, mild: 1-36, moderate: 37-72, severe: 73-108.
Mucus membrane score (MM) = area score + severity Score;
*Grade; free: 0; mild: 1, 2; moderate: 3, 4; severe: 5, 6.
Total score = cutaneous score + MM score.

Al Aini Hospital. In addition, twenty normal individuals with no known systemic, psychological, or dermatological diseases were included as controls.

Assessment of QOL, prevalence of depression and the level of IL-6

All participants were subjected to assessment of their psychiatric profile using Hamilton Depression Rating Scale (HDRS) (10) and Beck depression inventory (BDI) (11) (Arabic Version). Additionally, patient QOL was assessed via the Dermatology Life Quality Index (DLQI) as illustrated in Table 2 and B-Quality of life questionnaire QOL (12) which consists of 30 questions to assess somatic problems, thinking problems, mood problems, social stressor, economic problems, and special problems. The test was translated and standardized by Akram Kamal to be used in an Arabic version.

Three mL venous blood samples were collected by venipuncture from all participants. Blood was subjected to clot. Subsequently, each blood sample was centrifuged to separate serum. Serum samples were kept at -20 °C in Eppendorf tubes until being processed for IL-6 estimation. Serum IL-6 was determined for both patients and controls using the ELISA kit (Ani Biotech Orgenium Laboratories Business Unit Tiilitie 3FIN-07120 Vantaa-FINLAND).

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Mann-Whitney U test for independent samples. For comparing categorical data, the Chi-square (x^2) test was performed. Exact test was used instead when the expected frequency was less than 5. Correlation between various variables was assessed using Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. Multivariate analysis was used to test for the preferential effect of the selected important independent variable(s) on IL-6 levels in PV cases. P values less than 0.05 were considered statistically significant. All statistical calculations were performed using SPSS the computer program (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA), release 15 for Microsoft Windows (2006).

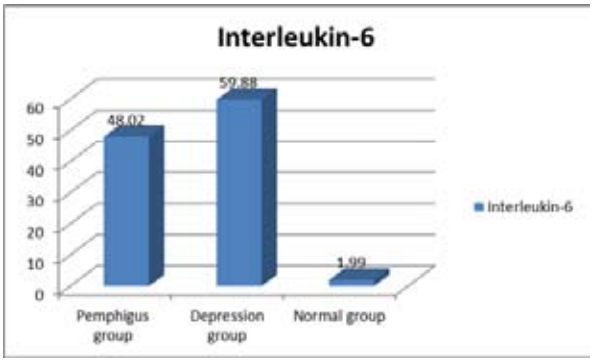

Figure 1. Serum Interleukin-6 in the three study groups.

RESULTS

The present study included 22 patients with PV, 5 men (22.7%) and 17 women (77.3%). Their age ranged from 17-75 years with a mean of 43.14 years ± SD 12.63. The duration of disease ranged from 1 month – 12 years with a mean of 2.24 years ± SD 34.46.

Table 2. Scoring and Interpretation of Dermatology Life Quality Index (DLQI) (12)

10 questions, each question answer is scored as follows	
Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 6: unanswered	scored 0
Question 7: "prevented work or studying"	scored 3
The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0 and interpreted as follows	
0-1	No effect at all on patient's life.
2-5	Small effect on patient's life.
6-10	Moderate effect on patient's life
11-20	Very large effect on patient's life
21-30	Extremely large effect on patient's life

DLQI: Dermatology Life Quality Index

Table 3. Prevalence and degree of depression in the three study groups

			Group			Total
			Pemphigus	Depression	Normal	
Depression	No	Count	9	0	14	9
		% within Group	40.9%	0.0%	70%	20.9%
	Yes	Count	13	21	6	34
		% within Group	59.1%	100.0%	30%	79.1%
Total		Count	22	21	20	43
		% within Group	100.0%	100.0%	100.0%	100.0%
			Group			P value
			Pemphigus	Depression	Normal	
Degree of depression	Depression	Count	13	21	6	P<0.001*
		% within Group	59.1%	100%	30%	
	Mild	Count	3	0	6	
		% within Group	13.6%	0.0%	30%	
	Moderate	Count	5	12	0	
		% within Group	22.7%	57.1%	0%	
	Severe	Count	5	9	0	
		% within Group	22.7%	42.9%	0%	

* P value <0.05 is statistically significant

Fourteen (64%) of the patients were recurrent cases and 8 (36%) were newly diagnosed. Twelve patients (54.5%) presented with mucocutaneous lesions, while ten patients (45.5%) presented with mucosal lesions. None of the patients had cutaneous lesions only (0%). PAAS ranged from 3.5 to 38.6 in mucocutaneous lesions with mean 12.64 ± SD 11.49, and this was translated into (8.3%) moderate and (91.7%) mild cases and ranged from 2 to 3 in mucosal lesions with mean 2.6 ± SD 0.516, with (60%) moderate and (40%) mild cases.

Twenty one patients belonging to the depression group were also included as controls, eight of whom were men (38.1%) and 13 women (61.9%), with age ranging between 23-62 years with a mean of 40.81 years ± SD 10.93. The duration of their depression ranged from 6 months to 5 years with a mean of 1.9 years ± SD 16.06. Sixteen (76%) of the patients were in remission and exacerbation, and 5 (24%) were newly diagnosed. Regarding the healthy controls, five were men (25%) and 15 were women (75%), with age ranging from 22 to 57 years with a mean of 33.15 years ± SD 9.85. Regarding smoking, 2/22 (9.1%) patients with PV, 7/21(33.3%) depressed patients, and 2/20 (10.0 %) normal controls were smokers (P>0.05). The prevalence and degree of depression among the PV group, depression group, as well as in the control group are shown in Table 3.

All (100%) included PV had a negative effect on their DLQI. Eleven patients (50%) had extremely large effect on their life, and 11 patients (50%) had very large effect on their life. As regards the QOL index, the worst score was recorded among the PV group (P<0.001) with a mean of 15.318 ± SD 4.79 and depression group (P<0.001) with a mean 18.095 ±SD 4.43. There was also significant difference between pemphigus and depression groups (P=0.026). The best score was recorded among normal controls, with a mean of 32.65±SD 2.059, with a significant difference in comparison to other groups (P<0.001).

There was a significant difference in IL-6 between the three study groups (P=0.046) (Figure 1). IL-6 level was highest in the depression group (Range 2-356, mean±SD 59.88±111.087) and lowest in the normal controls (Range 1-3.60, mean±SD 1.99±0.804). IL-6 was non-significantly elevated in the pemphigus group (Range 1-224, mean±SD 48.02±70.819), when compared with the control group (P=0.056) and there was no significant difference when compared with the depression group (P=0.125). There was significant difference in IL-6 between the depression group and control (P=0.039).

Dermatology life quality index was significantly worse in the depressed pemphigus subgroup (N=13) (mean 23.08 ± SD 3.52), when compared with the non-depressed pemphigus subgroup (N=9) (mean 16.78 ± SD 5.14) (P=0.006). QOL questionnaire results were significantly worse in the depressed pemphigus subgroup (N=13) (mean 12.31 ± SD 2.59) when compared with the non-depressed pemphigus subgroup (N=9) (mean 19.67 ± SD 3.77) (P<0.001). IL-6 was

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non-significantly elevated in the depressed pemphigus subgroup (N=13) (mean 57.15 ± SD 72.908) when compared with the non-depressed pemphigus subgroup (N=9) (mean 34.83 ± SD 69.719) (P=0.095).

The degree of depression in the pemphigus group showed a significant positive correlation with cutaneous score (P<0.001), mucous membrane score (P=0.002), and total PAAS (P<0.001) and a significant negative correlation with the disease duration (P=0.019). Similarly, the DLQI in the pemphigus group showed a significant negative correlation with disease duration (P=0.022) and the DLQI showed a significant positive correlation with degree of depression (P=0.003), cutaneous score (P=0.006), mucous membrane score (P=0.019), and total PAAS (P=0.015). IL-6 showed a significant correlation with cutaneous score (P=0.030).

In the depression group, a statistically significant correlation was found between IL-6 and disease duration (P=0.015), in addition to a significant correlation between degree of depression and QOL (P<0.001). No significant correlations were otherwise detected between any of the assessed parameters.

DISCUSSION

The current study adds PV to the long list of dermatological diseases that could be influenced by or influence the QOL of the affected patient. To our knowledge, there are no previous studies that investigated the relation between the QOL, depression, and cytokine level in patients with PV. Our assumption that pemphigus is a psychocutaneous interrelated disease is based on the deteriorated DLQI in the included 22 patients with pemphigus, where 50% had an extremely large effect on their life and 50% showed a very large effect on their life. Furthermore, the QOL questionnaire results were significantly worse in the pemphigus group compared with both the depression group and the control group. This finding was also reported in previous studies (13,14).

An important finding in our study was more impairment of QOL in patients with recent onset of the disease, i.e. DLQI in newly diagnosed patients with pemphigus compared with DLQI for recurrent cases. Although QOL is expected to get worse over time, adaptation of the patients to their condition may be responsible for a relatively poorer QOL in the early stages of PV in our patients. Over a certain period of time, controlling the symptoms, learning about different aspects of the disease, and coping more efficiently with the disease and therapies may significantly improve the patients' health status. This finding was similar to another report (15).

In our study, depression was detected in most included patients with pemphigus (59.1%), and this finding has been previously reported (15,16). Moreover, QOL in the depressed pemphigus group was significantly deteriorated compared with the non-depressed pemphigus group according to both the DLQI and QOL questionnaires. A similar finding was found by Arbabi *et al.* (17), but whether the depression was a key factor which lowered their QOL scores or the other way around is a question that remains to be answered. Either way, it raised a red flag about the importance of a good psychiatric analysis for patients with pemphigus to be able to evaluate their psychiatric illness at an early stage.

On the other hand, 40.9% of the included patients with pemphigus in our study were not depressed, further confirming the need for proper psychiatric assessment, as it indicated that not all patients with pemphigus need antidepressant medications.

There was significant correlation between PAAS and degree of depression. The correlation between PAAS and DLQI was also significant. This can go in one of two directions; either clinical impairment leads to QOL deterioration, which is quite logical, or QOL deterioration leads to clinical impairment. IL-6 was investigated as a possible culprit for this connection, and to our knowledge this was the first study that tried to find a link between IL-6, depression, and PV.

The pathogenesis of pemphigus disease is frequently characterized by pro-inflammatory cytokine production such as TNF-α, IL-1, or IL-6 as strong players involved in acantholysis (18). Evidence for the role of raised inflammatory markers in depression has been building over the last 20 years. In the current study, there was a significant difference in IL-6 between the three studied groups and was higher in the depression group and higher in the pemphigus group than normal controls, which might be explained by the role of IL-6 as one of inflammatory cytokines in pathogenesis of depression and pemphigus (18). IL-6 was non-significantly elevated in the pemphigus group when compared with the control group, which might be explained by small sample size and the role of cytokines other than IL-6 incriminated in pemphigus pathogenesis.

In our study, there was an absence of a significant correlation between IL-6 on one hand and PASS as well as DLQI on the other hand. The multifactorial nature of the studied disease offers an explanation to the absence of such correlation. However, Narbutt *et al.* (4) showed that IL-6 serum concentration was significantly higher in the patients presenting the active stage of PV when compared with the control group.

CONCLUSION

We recommend taking QOL changes into account during the initial clinical assessment of patients with pemphigus. Physicians must be aware of the presentation of depression and anxiety among such patients. Proper management of these symptoms can improve their QOL considerably. Antidepressant drugs should not be obligatory in all pemphigus cases, but only in selected ones. Further studies are needed to confirm the role of IL-6 in pemphigus pathogenesis.

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