ORIGINAL ARTICLE

Evaluation of the Relationship between Pemphigus Vulgaris Severity and the Serum Levels of IL33 and anti-Desmoglein-3 Antibody

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ABSTRACT

Background*: Pemphigus is a potentially life-threatening autoimmune disorder affecting both skin and mucosa. Clinically, it is characterized by blister formation and erosions, and histologically, by acantholysis. Pemphigus vulgaris (PV) is the most common type within the pemphigus groups. The pathogenesis of pemphigus includes the presence of autoantibodies directed against desmosomal proteins like desmoglein on the cell surface of keratinocytes, which are critical for keratinocyte adhesion and epidermal structural integrity. In addition, PV pathogenesis involves a dysregulated immune response, with multiple involved cytokines, including interleukin-33 (IL-33).* ***Objective****: To evaluate the relationship between the severity of PV and IL-33 and anti-Dsg3 antibodies serum levels.* ***Methodology****: A case-control study was conducted on fifty patients diagnosed with PV and fifty healthy controls matched in age and sex. Clinical evaluation was performed on each patient, and the Pemphigus Vulgaris Activity Score (PVAS) was used to classify the patients into three distinct categories according to the PV severity. Serum samples were obtained from both patients and control participants and analyzed quantitatively for IL-33 and anti-Dsg3 antibodies using ELISA.* ***Results****: Serum levels of IL-33 and anti-Dsg-3 were significantly higher in PV patients compared to healthy controls, with a significant association with PV severity.* ***Conclusion****: IL-33 and anti-Dsg-3 are useful markers for the evaluation of PV activity.*

INTRODUCTION

The term pemphigus is derived from the Greek word pemphix, meaning blister or bubble[1]. Pemphigus is a potentially life-threatening autoimmune disorder that clinically presents with blisters and erosions affecting both skin and mucous membranes and histopathologically by acantholysis (separation and rounding up of epidermal cells) as a result of loss of epidermal keratinocyte adhesion. It poses a therapeutic challenge for the clinician and is associated with a high rate of mortality [2].

The pemphigus group of diseases has been classified into multiple forms, based on clinical, histopathological, and immunological characteristics. The main forms are Pemphigus vulgaris (PV) and Pemphigus foliaceus (PF), while IgA Pemphigus, Pemphigus herpetiformis, and Paraneoplastic pemphigus represent the non-classical forms[3].

The pathogenesis of pemphigus involves B-cell activation and production of IgG autoantibodies against the desmosomal adhesion proteins, desmoglein 3 (Dsg3) and/or Dsg1, on epidermal keratinocytes, which is mediated by Dsg3-reactive CD4+ T-helper 2 cells cytokines secretion as IL-4. The major immunoglobulin isotype present in the pool of Dsg3-specific autoantibodies in PV is IgG4 in acute disease and IgG1 in chronic active and in some patients in remitting disease [4].

Anti-Dsg3- autoantibodies act by steric hindrance that leads to loss of desmosomal integrity and blister formation by several mechanisms. Dsg-specific IgG autoantibodies alter major cellular signaling events involving p38 MAPK (responsible for intermediate filament organization and thereby maintenance of the desmosomal structure), protein kinase C (PKC) (responsible for induction of Dsg3 depletion from the desmosome), c-Jun N-terminal kinases (JNK), RhoA and caspases 3, 6, 8 and 9 (responsible for keratinocyte apoptosis)[5].

Interleukin-33 (IL-33) initially referred to as DVS27, is a gene upregulated in vasospastic cerebral arteries after subarachnoid hemorrhage[6]. DVS27 was reidentified as interleukin-33 in 2005 and subsequently recognized as the 11th member of the IL-1 cytokine family[7]. Suppression of tumorigenicity 2 (ST2), also

known as IL-1R4, functions as an IL-33 receptor composed of heterodimeric fragments, including ST2 and IL-1R accessory protein (IL-1RAcP)[8]. IL-33 may function as an alarm signal (alarmin) released in the extracellular space after cellular damage or mechanical injury during trauma and/or infection, as well as sterile insults of both endogenous and exogenous sources to alert the immune system of cell or tissue damage[9].

IL-33 acts on a broad range of target cells, involving adaptive and innate immune cells, thereby influencing both branches of the immune system [10]. IL‑33 has a dual role in different diseases, depending on the specific immune mechanism of each disease pathogenesis. Its effects depend on the tissue context; it can facilitate the resolution of inflammatory responses, or infection‑induced tissue damage [11].

IL-33 is involved in various skin and autoimmune diseases. In atopic dermatitis (AD), it promotes type 2 inflammation and barrier dysfunction[12] and is overexpressed in psoriasis, activating immune responses[13]. Elevated IL-33 levels correlate with disease severity in systemic sclerosis (SSc)[14], systemic lupus erythematosus (SLE)[15,16], vitiligo[17], chronic spontaneous urticaria (CSU)[18], Henoch-Schönlein purpura (HSP)[19], rheumatoid arthritis (RA)[20], Kawasaki disease (KD)[21], and Vogt-Koyanagi-Harada (VKH) disease[22]. In contrast, bullous pemphigoid (BP) shows increased sST2 but undetectable IL-33[23]. IL-33 is locally expressed in allergic contact dermatitis (ACD)[24] and may contribute to localized scleroderma (morphea)[25] and oral lichen planus[26].

IL-33 and sST2 may have a remarkable role in the pathogenesis of PV, although their role is not well-recognized, their main role in the adaptive immune response is the enhancement of production of Th2 cytokines unknown and could be considered markers of disease activity and may not be used as specific marker[27].

The aim of the present study is to evaluate the relationship between the severity of PV and the serum levels of IL-33 and anti-Dsg3 antibodies.

METHODOLOGY

This case-control study was carried out on fifty patients diagnosed with PV and fifty healthy unrelated controls matched for age and sex, from the outpatient clinic of the Dermatology department at Mansoura University Hospital.

Inclusion criteria: newly diagnosed patients with PV who did not receive topical or systemic therapy and patients who experienced exacerbation while in remission for at least one month without immunosuppressive therapy. *Exclusion criteria;* Patients with concurrent autoimmune diseases that may alter IL-33 levels and patients on immunosuppressive therapy were excluded.

All patients were subjected to thorough history taking, including age, sex, duration of the disease, last time of any treatment received, and history of any other medical conditions and general and dermatological examination to exclude any associated autoimmune disease.

Diagnosis of PV depends on clinical and histopathological findings. Following a clinical evaluation of each patient, the PVAS **(table 1)** was used to classify the patients into three distinct categories according to the PV severity. Group A: Patients with mild disease (with a PVAS score of six out of 18 points), group B: Patients with disease of moderate severity (a PVAS score of 7–12 out of 18 points), and group C: Patients with severe disease (with a PVAS score of ≥ 13 out of 18 points).

Both patients and controls were subjected to blood sampling for detection of IL-33 and anti-Dsg3 antibodies: 3 ml of venous blood were withdrawn from each subject under complete aseptic conditions. The blood was left for at least 15 minutes for clotting, and then separation of serum from blood cells was done by centrifugation. The obtained serum of each sample was divided into two aliquots and frozen at – 20º C until completion of sample collection for ELISA for the detection of both IL-33 and anti-Dsg3 antibodies.

Ethical Consideration:

Informed verbal consent was obtained from each participant sharing in this study. Approval of the managers in the health care facility in which the study was obtained. Confidentiality and personal privacy of patients were respected throughout the study. The collected data was used for scientific purposes only. The study protocol was submitted for Institutional Research Board (IRB) approval. Code number: MS.17.04.30.

Table 1: Pemphigus Vulgaris Activity Score (PVAS) [28].

PVAS= skin disease score + mucosal disease score, range 0-18				
Skin disease score = Ts× (Ns +Ds +Ss)		Point	Description	Max 11
Ts	Type of skin lesion	1	Blister or bulla	1
		0.5	Crusted lesions	
		0	Only pigmentation change.	
Ns	Number of skin lesion	2	More than 20 bullae	2
		1	Twenty or less blisters (≤20)	
Ds	Distribution of skin lesion. One point for each anatomical area	1	Scalp	8
		1	Face	
		1	Neck	
		1	Trunk	
		1	Each limb (0-4 for no limb to four extremities)	
Ss	Nikolsky's sign: pressure induced blister	1	On the unaffected area	1
		0.5	Around the lesions	
		0	None	
Mucosal disease score = Tm× (Nm + Dm)			7	
Tm	Type of mucosal lesion	1	Blister or bulla	1
		0.5	Ulceration	
		0	None	
Nm	Number of mucosal lesions	2	More than 2 bullae (>2).	2
		1	One or two blisters	
Dm	Distribution of mucosal lesion. One point for each anatomical area	1	Oral cavity and/ or pharynx	5
		1	Eyes	
		1	Upper airways	
		1	Anus	
		1	Genital area	
Total PVAS score = [Ts × (Ns+ Ds+ Ss)] + [Tm× (Nm+ Dm)]			18	

Statistical analysis and data interpretation:

Data analysis was performed by SPSS software, version 25 (SPSS Inc., PASW statistics for Windows version 25. Chicago: SPSS Inc.). Qualitative data were described using numbers and percentages. Quantitative data were described using median (minimum and maximum) for non-normally variables and mean± Standard deviation for normally variables after testing normality using the Kolmogorov-Smirnov test. The significance of the obtained results was judged at the ≤0.05. Mann-Whitney U and Kruskal Wallis test were used to compare between two and multiples studied groups, respectively for non-normally distributed data. Spearman's rank-order correlation was used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and/or ordinal variables. The receiver operating characteristics curve (ROC curve) was used to calculate the validity (sensitivity & specificity) of continuous variables with the calculation of the best cut-off point. Predictive values and accuracy are assessed using cross-tabulation. Multiple linear regression was used to assess predictors of continuous, normally distributed outcomes with the calculation of R2.

RESULTS

This study was carried out on fifty PV patients and fifty age and sex matched healthy controls. The numbers of male patients were 28 (56%), while female patients were 22 (44%)**.** The patients age ranged from 23-76 years with a mean value± SD of 44.92±11.68 **(table 2).**

Among the study, 28 patients (56%) with newly diagnosed PV and had not received any topical or systemic therapy. Additionally, 22 patients (44%) experienced exacerbation of their condition while in remission for at least one month without the use of immunosuppressive therapy.

As regards the PVAS, 23 patients (46%) showed mild disease (group A), 20 patients (40%) showed severe disease (group C) while 7 patients (14%) showed moderate disease (group B), with the mean PVSA score of 10.27±4.42 and median 10.0 (6-18) **(table 3).**

Table 2: Demographic characteristics of the studied groups

		Cases group		Control group		Test of significance
		N=50	%	N=50	%	
Age / years	**Mean ±SD (min-max)**	44.92±11.68 (23-76)		41.52±10.66 (19-62)		t=1.52 p=0.132
Sex	**Males**	28	56.0	27	54.0	χ^2=1.97
	Females	22	44.0	23	46.0	p=0.161

t: Student t test, χ^2: Chi-Square test, p: p-value

Table 3: Pemphigus vulgaris severity score of the patient group

	Mean ±SD	Median (min-max)
Pemphigus vulgaris severity score	10.27±4.42	10.0(6-18)
Pemphigus vulgaris severity score grade	**Total no=50**	**%**
Mild (group A)	23	46.0
Moderate (group B)	7	14.0
Severe (group C)	20	40.0

SD: standard deviation

Differences in IL-33 and anti-Dsg3 levels were not significantly influenced by age groups, sex, or treatment status **(table 4).** In PV patients < 45 years, IL-33 levels ranged from 6.14 to 39.2 with a median of 17.62, while anti-Dsg3 levels ranged from 2.27 to 12.48 with a median of 5.32. In PV patients ≥ 45 years, IL-33 levels ranged from 5.25 to 85.07 with a median of 17.16, whereas anti-Dsg3 levels ranged from 2.92 to 24.3 with a median of 5.38. In males, IL-33 levels ranged from 5.61 to 85.07 with a median of 18.98, and anti-Dsg3 levels ranged from 2.27 to 24.3 with a median of 5.38. In females, IL-33 levels ranged from 5.25 to 59.58 with a median of 16.98, and anti-Dsg3 levels ranged from 2.92 to 14.57 with a median of 5.31. IL-33 levels in untreated patients ranged from 5.25 to 85.07 with a median of 18.02, while anti-Dsg3 levels ranged from 2.27 to 24.3 with a median of 5.42. In patients with at least one month of remission without immunosuppressive therapy, IL-33 levels ranged from 5.61 to 59.58 with a median of 17.62, and anti-Dsg3 levels ranged from 3.64 to 11.14 with a median of 5.25.

The IL-33 and anti-Dsg-3 antibody levels in PV patients were significantly elevated compared to healthy controls, demonstrating a statistically significant difference. IL-33 levels in PV patients ranged from 5.25 to 85.07 ng/dL, with a median value of 17.62 ng/dL, whereas in the control group, IL33 levels ranged from 3.08 to 7.69 ng/dL, with a median of 4.97 ng/dL. Similarly, the anti-Dsg-3 antibody levels in PV patients ranged from 2.27 to 24.3 ng/dL, with a median of 5.38 ng/dL, whereas in the control group, levels ranged from 1.0 to 7.54 ng/dL, with a median of 3.80 ng/dL **(table 5).**

Table 4: Relation between IL-33 and Dsg3 with demographic characteristics

		IL-33 Median (min-max)	Test of significance	Anti Dsg-3 Median (min-max)	Test of significance
Age / years	**<45**	17.62 (6.14-39.2)	Z=0.117 P=0.907	5.32 (2.27-12.48)	Z=0.0718 P=0.472
	≥45	17.16 (5.25-85.07)		5.38 (2.92-24.3)	
Sex	**Males**	18.98 (5.61-85.07)	Z=0.158 P=0.877	5.38 (2.27-24.3)	Z=0.317 P=0.751
	Females	16.98 (5.25-59.58)		5.31 (2.92-14.57)	
Last time receive treatment	**No**	18.02 (5.25-85.07)	Z=0.430 P=0.667	5.42 (2.27-24.3)	Z=0.391 P=0.696
	One month	17.62 (5.61-59.58)		5.25 (3.64-11.14)	

Z: Mann Whitney U test, P: P-value

Table 5: Comparison of IL-33 and anti-Dsg3 between cases & control groups

	Cases group	Control group	Test of significance
IL-33 Median (min-max)	17.62 (5.25-85.07)	4.97 (3.08-7.69)	Z=7.92 P<0.001*
Anti-Dsg3 Median (min-max)	5.38 (2.27-24.3)	3.80 (1.0-7.54)	Z=3.90 P<0.001*

Z: Mann Whitney U test, P: P-value. *Statistically significant

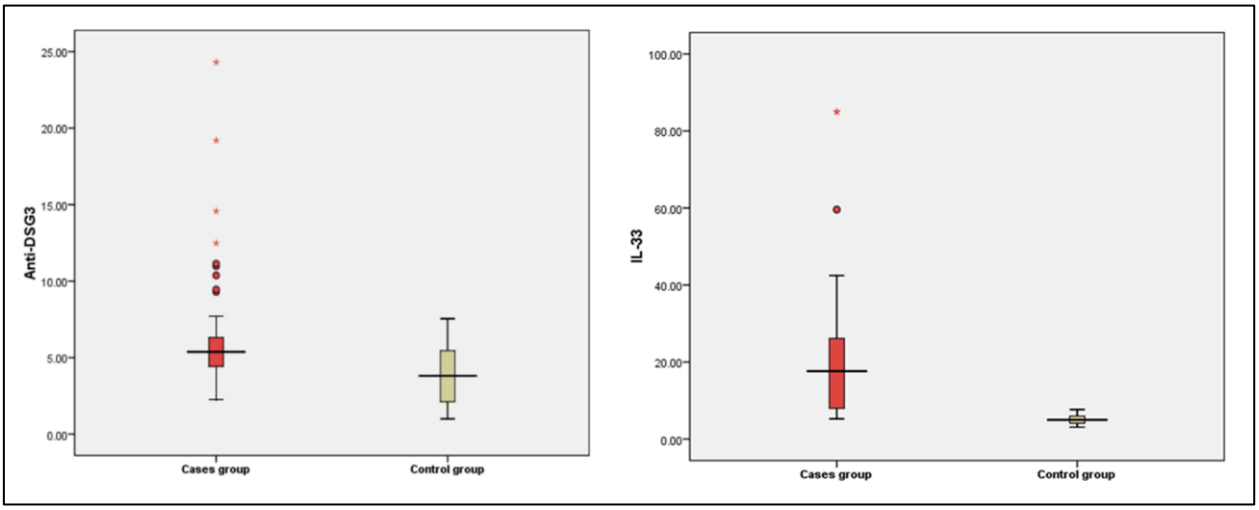

Fig. 1: Box& Whisker plot showing median IL-33 (right) and anti-Dsg-3 (left) among studied groups.

The Box & whisker plot **(figure 1)** represents the distribution of a dataset, its central tendency, spread, and outliers. The plot on the right shows that IL-33 levels were elevated in the cases group compared to the control group. The larger Box and longer Whiskers in the cases group suggest higher variability in IL-33 levels, and the presence of outliers indicates that some patients show extremely elevated IL-33 levels, while the control group has low and consistent IL-33 levels, suggesting minimal variability. The plot on the left shows that the cases group exhibits higher anti-Dsg-3 levels than the control group, with greater variability and the presence of several outliers in the cases group, indicating a wider range of values, while in the control group, IL33 levels showed less variation with no outliers.

IL-33 and anti-Dsg3 levels showed no significant correlation with disease duration ($p = 0.703$ and $p = 0.910$). However, IL-33 showed a strong positive correlation with PVAS ($r = 0.946$, $p < 0.001$), skin score ($r = 0.895$, $p < 0.001$), and mucosal score ($r = 0.728$, $p < 0.001$). Similarly, anti-Dsg3 positively correlates with PVAS significantly ($r = 0.710$, $p < 0.001$), skin score ($r = 0.722$, $p < 0.001$), and mucosal score ($r = 0.634$, $p < 0.001$). These findings suggest that IL-33 and anti-Dsg3 were strongly associated with disease severity but not with disease duration **(table 6).**

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Table 6: Correlation between IL-33 and Anti-Dsg3 with disease duration, PVAS, skin score, and mucosal score.

		IL.33	Anti-Dsg3
Duration (months)	r	- 0.055	- 0.016
	p	0.703	0.910
PVAS score	r	0.946**	0.710
	p	<0.001*	<0.001*
Skin score	r	0.895**	0.722
	p	<0.001*	<0.001*
Mucosal score	r	0.728**	0.634
	p	<0.001*	<0.001*

r: Spearman correlation coefficient,
P: P-value. *Statistically significant

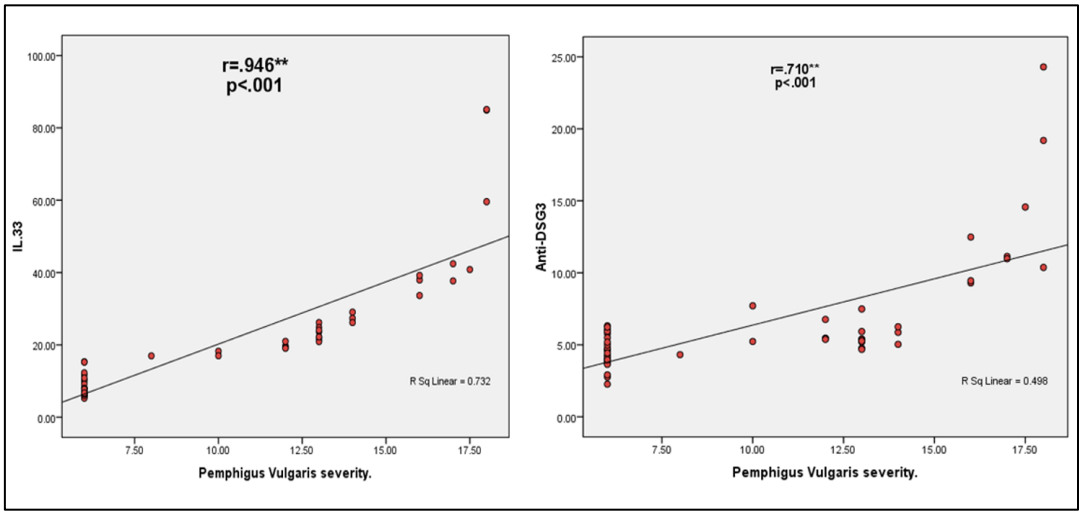

Fig. 2: Correlation between IL-33 and PV severity (left). Correlation between Anti-Dsg3 and Pemphigus Vulgaris severity (right).

Higher IL-33 and anti-Dsg-3 levels were associated with increased PV severity (**Figure 2**); Figure 2 (left side) showed a significant strong positive correlation between IL-33 levels and PV severity (r = 0.946, p<0.001). The R^2 value (0.732) indicates that 73.2% of IL-33 variation is explained by PV severity. Figure 2 (right side) also demonstrated a significant positive correlation (r = 0.710, p < 0.001). between anti-Dsg-3 levels and PV severity. The R^2 value (0.498) indicates that 49.8% of the variation in anti-Dsg-3 levels can be explained by PV severity.

The serum IL-33 levels were observed to be highest in patients with severe disease (Group C), with a median value of 28.19, followed by patients with moderate disease (Group B) with a median of 19.07, and patients with mild disease (Group A) with a median of 7.80. Similarly, the serum anti-Dsg-3 antibody levels were highest in patients with severe disease (group C), with a median value of 6.87, followed by patients with moderate disease (group B) with a median of 5.44, and patients with mild disease (group A) with a median of 4.42. Statistically significant difference was observed among the 3 groups, indicating a gradation in IL-33 and anti-Dsg-3 antibody levels corresponding to disease severity **(Table 7).**

Table 7: Relation between IL-33 and anti-Dsg3 with Pemphigus vulgaris severity score grade

Pemphigus vulgaris severity score grade	IL-33 Median (min-max)	Test of significance	Anti-Dsg3 Median (min-max)	Test of significance
Mild disease (Group A)	7.80 (5.25-15.33)	Kw=40.85 P<0.001*	4.42(2.27-6.32)	Kw*=18.97 P<0.001*
Moderate disease (Group B)	19.07 (16.97-20.97)		5.44(4.31-7.71)	
Severe disease (Group C)	28.19 (20.9-85.07)		6.87(4.69-24.3)	

KW: Kruskal Wallis test. *statistically significant

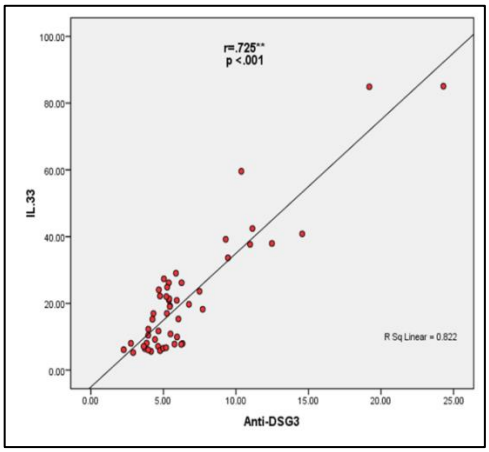

Fig. 3: Correlation between Anti-Dsg3 and IL33.

A strong positive correlation between anti-Dsg-3 and IL-33 levels was observed (r = 0.725, p < 0.001), suggesting that higher anti-Dsg3 levels are significantly associated with increased IL-33. The R^2 value (0.822) indicates that 82.2% of the variance in IL-33 levels can be explained by anti-Dsg3. This strong correlation implies a potential link between anti-Dsg3 autoantibodies and IL-33 **(figure 3).**

DISCUSSION

Since its discovery, IL-33 has emerged as a significant member of the IL-1 cytokine family that regulates both innate and adaptive lymphoid cell functions. Its production is triggered by various internal

and external stimuli across multiple cell types. While free IL-33 helps the host defend against pathogens, its dysregulation is associated with several skin diseases pathogenesis. Therefore, IL-33 neutralization may offer a promising therapeutic strategy [29].

Blister formation, the main feature of PV, is believed to arise from overproduction of cytokines and inflammatory mediators. IL-33 may be an important cytokine involved in PV pathogenesis, and its level could serve as a marker of the disease severity [30].

The present study aims to evaluate the relationship between the severity of PV and the serum levels of IL-33 and anti-Dsg3 antibodies, as detected using ELISA.

In the present study, 50 patients with PV were compared with 50 age and sex-matched healthy controls. According to PVAS, PV patients were classified into three distinct categories based on disease severity to mild, moderate, and severe compared to the study done by Tirado- Sánchez et al.,[27] who categorized sixty patients with active PV according to the Pemphigus Vulgaris Activity Score (PVAS) into two groups but patients with disease of moderate severity were excluded. In the study done by Bakr et al.,[30] 40 PV patients were included and 36 healthy controls matched by age and sex, with disease severity assessed using the Pemphigus Disease Area Index (PADI).

In a study by Chams-Davatchi et al.[31] evaluating PVAS in 50 PV patients. The results proved that PVAS is a reliable, objective and easy-to-use scoring system.

In 2012, a cross-sectional study was done on PV patients with clinical assessment of pemphigus lesions. A total of 100 patients were evaluated using PDAI, Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), and PVAS. Serum concentrations of anti-Dsg1 and anti-Dsg3 antibodies were measured using ELISA. Among the assessment tools, the PDAI demonstrated the highest interrater reliability, followed by the ABSIS and PVAS. Similarly, the PDAI showed the highest convergent validity, with the PVAS and ABSIS following in order [28].

In the present research, it was found that serum level of IL-33 was significantly higher in patients compared to healthy control subjects and a significant positive correlation between the level of IL-33 and PVAS with a higher level among patients with severe PVAS which is similar to the result conducted by Tirado- Sánchez et al.[27] and Bakr et al.,[30].

Madkour and EL Refaie[32] observed a statistically significant increase in IL-33 levels in both saliva and serum of patients with oral PV. They further reported that serum IL-33 levels showed a significant reduction in all patients after corticosteroid therapy.

Compared to the Brazilian study performed by Timoteo et al.[33] which included 20 patients with PV and 20 age- and sex-adjusted healthy controls, all patients were receiving treatment with glucocorticoids, prednisolone, and dapsone. The study found no significant differences in IL-33 levels between PV patients and healthy controls. The observed variations in the cytokine profiles may be attributed to the impact of previous treatments, and factors such as racial or ethnic differences, genetic variability.

Unlike our study, Tavakolpour et al.[34] conducted a systematic review to assess the effective roles of many cytokines in both PV and PF. They analyzed 57 studies investigating 26 different cytokines. The authors emphasized the uncertainty about the exact effect of IL-33 on these disorders and treatment with immunosuppressive therapy may potentially reduce IL-33 levels.

In the present study, the anti-Dsg-3 antibodies serum levels were higher in PV patients compared to healthy controls and demonstrated a significant correlation with disease severity.

In a study correlating the anti-Dsg1 and anti-Dsg3 antibodies with the severity of PV by Delavarian et al.[35] the antibody titers of nineteen newly diagnosed PV patients were measured at the time of diagnosis as well as 4th and 8th weeks following treatment. The relationship between antibody levels and the severity of oral and skin lesions was assessed. They found a significant correlation between the severity of cutaneous lesions and anti-Dsg1 titers in all visits, while mucosal lesion severity was associated with anti-Dsg3 titers only at the third visit.

The relationship between Dsg1 and Dsg3 antibody levels and the severity of PV and PF was compared in a cross-sectional study, in which blood samples from 38 patients with PV and 6 patients with PF were analyzed using ELISA. They utilized a grading scale ranging from 0 to 3 to assess the severity of skin and mucosal involvement. The results demonstrated a statistically significant correlation between elevated Dsg3 and Dsg1 antibody titers and the severity of skin involvement in both PV and PF patients[36].

By Daneshpazhooh et al.[37] a study was directed at the Pemphigus Research Unit of Razi Hospital in Tehran, Iran, seventy-three PV patients were tested using ELISA to identify autoantibodies against Dsg1 and Dsg3. The antibody levels were analyzed in relation to the clinical phenotype and the severity of both skin and oral manifestations. The ELISA was repeated on 18 patients after treatment and subsequent remission. The findings indicated that anti-Dsg1 antibody levels were associated with the severity of skin lesions only, whereas anti-Dsg3 antibody levels showed a significant correlation with the severity of both skin and oral lesions. A considerable reduction in both anti-Dsg1 and anti-Dsg3 antibody levels was observed after treatment and clinical remission.

A retrospective study involving 187 PV patients was done to evaluate the effectiveness of anti-Dsg antibody levels as a marker for assessing the severity of PV. According to the PDAI score, the patients were

classified based on the disease severity into mild (0–8), moderate (9–24), and severe (≥ 25) categories. The findings revealed a significant positive correlation between Dsg1 and Dsg3 antibody levels and the PDAI score[18].

CONCLUSION

Based on the results of the current study, IL-33 and Dsg-3 showed a statistically significant increase in PV disease compared to healthy control with a significant increase in disease activity. The study concluded that IL-33 and Dsg-3 are useful markers for the evaluation of PV activity.

Recommendations: It is recommended to include the measurement of serum IL-33 levels as part of routine diagnostic and prognostic assessments in PV patients. IL-33 can serve as a biomarker for assessment of the disease severity and monitor disease progression. Furthermore, the detection of anti-Dsg3 autoantibody levels may add to the detection of IL-33 levels in assessing disease activity, particularly when additional corroborative evidence is required. Future studies are required for the detection of the usefulness of these biomarkers in larger populations and to investigate their potential role in guiding therapy. For instance, targeting IL-33-mediated pathways might offer a novel therapeutic approach that could decrease the disease severity and improve patient outcomes.

Declarations: Ethics Approval and Consent to Participate Mansoura University's Faculty of Medicine's Ethical Committee gave its approval for the study and the patient's participation. Ethics of Humanity was given the all-clear by the Mansoura University Faculty of Medicine's Ethics Committee.

Conflict of interest: The investigators declare no conflict of interest.

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