Relationship Between Pemphigus Vulgaris Severity and PCR-positive Herpes Simplex Virus

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Pemphigus vulgaris is a rare autoimmune skin disease. Although herpes simplex virus has been associated with autoimmune diseases, evidence regarding its association with pemphigus vulgaris exacerbations is scarce. This retrospective cohort study aimed to characterize the epidemiological and clinical features of patients with pemphigus vulgaris who were herpes simplex-positive, compared with those who were herpes simplex-negative, during disease onset. Of 62 patients with pemphigus vulgaris who underwent PCR testing for herpes simplex virus, 25 (40.3%) were positive, with a mean age of 56.1±15.5 years; 35.5% were male. The herpes-positive group had significantly elevated levels of C-reactive protein, Pemphigus Disease Activity Index score, and shorter time to relapse. The time to remission, number of exacerbations per year, and remission status were non-significantly elevated in the herpes-positive group. Thus, routine testing lesions from patients with pemphigus for herpes simplex virus should be performed. If positive, antiviral treatment should be initiated; and preventive antiviral treatment should be considered in severe cases.

Key words: pemphigus vulgaris; herpes simplex; disease exacerbation; acyclovir.

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Pemphigus vulgaris (PV) is a rare autoimmune skin disease that occurs mainly between the ages of 40 and 60 years (1, 2). The disease is characterized by blisters and erosions that involve only the mucous membranes or mucous membranes and skin (3, 4). The PV mucosal variant is associated with formation of IgG antibodies directed against desmoglein-3 (DSG3), while the mucocutaneous PV variant is associated with IgG antibodies directed against DSG3 and desmoglein-1 (DSG1). The binding of antibodies leads to acantholysis and the formation of blisters which tend to easily rupture, resulting in painful erosions that impair quality of life and cause secondary infections with increased morbidity and mortality (1, 5, 6). Ultraviolet radiation, X-rays, drugs, neoplasms, pregnancy, emotional stress, vaccinations, nutritional issues, and viruses are exogenous factors which have been linked to the aetiopathogenesis of PV. Herpes simplex virus (HSV) has been reported to be associated with PV and might influence initiation and exacerbation of PV (7–9). Even though current literature emphasizes an association between herpes viruses, especially HSV 1 and 2, and autoimmune diseases, such as autoimmune encephalitis post-herpes simplex (10), there is insufficient evidence regarding the relationship between HSV and PV (11, 12).

The aim of this study was to characterize the clinical and epidemiological features of patients with PV during the onset of their disease, who were positive for HSV by PCR testing of active lesions, and to compare them with those who were negative for HSV by PCR testing of active lesions.

MATERIALS AND METHODS

This was a retrospective cohort study. The patients were diagnosed and treated at the dermatology department and outpatient clinic of the Sheba Medical Center, Tel Hashomer, Israel, from 2009 to 2021, and at the dermatology department and outpatient clinic of Sourasky Medical Center, Tel-Aviv, Israel, from 2016 to 2021.
Patient data were collected from the electronic medical records (Chameleon) of each of these hospitals. The study population comprised patients with PV admitted during the onset of their disease, and clinical and laboratory findings were compared between HSV-positive and HSV-negative patients. Disease activity was measured with the Pemphigus Disease Activity Index (PDAI) (13). It is notable that, prior to PV onset, all patients did not require a PCR or serological test for HSV; therefore, their HSV status was not documented in their medical records. Nevertheless, the presence of previous HSV infection was specifically examined during anamnesis and documented during data collection.

Patients with PV admitted during onset of the disease were diagnosed according to the established criteria (14): (i) clinical evaluation: skin blisters and/or mucosal erosions, and (ii) histological evaluation: a skin or mucosal biopsy positive for intra-epidermal separation (acantholysis); and (iii) direct immunofluorescence: identification of auto-antibodies typical of PV in a skin biopsy

Inclusion criteria were: (i) patients with confirmed PV fulfilling the criteria cited above; (ii) documented PV onset with no prior immunosuppressive treatment to avoid bias of HSV exacerbation due to immunosuppression unrelated to PV; and (iii) PCR testing for HSV during onset.

Exclusion criteria were: (i) no documentation of the exact date of PV onset, (ii) no PCR testing for HSV during onset of PV, and (iii) treatment non-naive (received prior treatment for PV) (Fig. 1).

The remission status was documented at each follow-up, based on the consensus statement on the definitions of disease, endpoints, and therapeutic response for pemphigus (15), as follows: (i) complete remission off therapy; (ii) complete remission on therapy; (iii) partial remission off therapy; (iv) partial remission on therapy.

**Herpes simplex virus PCR test**

HSV-DNA-detection was analysed using tissue scrapings of the oral cavity sent for conventional diagnostic PCR. An ABI PRISM 7500 sequence detection system (Applied Biosystems, Foster City, CA, USA) was used for amplification and detection of the genomic DNA-sequences. DNA was purified from 0.2 ml swab samples using an automatic DNA extractor according to the manufacturer’s instructions. Extracted DNA was eluted in 50–100 ml elution buffer and stored at −20°C pending analysis. HSV genome detection from clinical swabs was performed using TaqMan based RT-PCR, as described previously (16). All HSV-positive patients were treated following the Centers for Disease Control and Prevention (CDC) treatment protocol (17), which was administration of acyclovir 400 mg orally 3 times a day for 7–10 days or valacyclovir 1 g orally twice a day for 7–10 days. Patients were divided into 2 groups: PV-patients with a positive PCR test for HSV during onset and PV-patients with a negative PCR test for HSV during onset. Ethical approval (SMC-7172-09) was provided by the Institutional Review Board (IRB) and the study was conducted in accordance with the principles of the Declaration of Helsinki. Patient consent was waived due to the retrospective nature of the study.

### Statistical analysis

Continuous variables are described as means and standard deviations, and categorical variables are presented as proportions and percentages. A comparative analysis was performed between HSV-positive and HSV-negative patients with PV using the Student’s t-test for continuous variables and Pearson’s χ² test for categorical variables. Time to first relapse is presented using Kaplan–Meier curves, and p-values were calculated using the log-rank test. All statistical tests were 2-tailed, and p-values < 0.05 were considered significant. Data were analysed using R software and the Python programming language.

### RESULTS

The database search yielded 178 patients with PV, of whom 102 were tested for HSV via PCR. Among these, 62 were tested during their PV onset and comprised the study group. The male-to-female ratio was 0.55:1, with 22 men (35.48%) and 40 women (64.52%) and a mean age of 56.1 ± 15.5 years. Among all 62 patients with PV, 18 had mucosal involvement only (29%), and 44 had skin and mucosal involvement (71%). The mean follow-up time was 35.7 ± 26.9 months. HSV infection was confirmed by PCR in 25 of 62 patients (40.3%).

There were no statistically significant differences regarding baseline characteristics, including age, background diseases, and follow-up time, between the HSV-positive and HSV-negative PV-patients. There was no difference between the groups in terms of disease involvement, measured by involvement of mucosa only or mucosa and skin (Table I).

### Table 1. Demographic and clinical data of herpes simplex-positive patients compared with herpes simplex-negative patients

| Parameter                             | HSV-positive (n = 25) | HSV-negative (n = 37) | p-value |
|---------------------------------------|-----------------------|-----------------------|---------|
| Age, years, mean ± SD                 | 57.92 ± 12.91         | 54.95 ± 16.75         | 0.46    |
| Sex (male), n (%)                     | 9/25 (36)             | 13/37 (35.14)         | 0.84    |
| Positive-PMH, n (%)                   | 10/25 (40)            | 16/37 (43)            | 0.99    |
| Time of follow up, months, mean ± SD  | 34.56 ± 24.9          | 36.51 ± 27.77         | 0.78    |
| Disease involvement                   |                       |                       |         |
| Mucosa only, n (%)                    | 6/25 (24)             | 12/37 (32.43)         |         |
| Mucosa and skin, n (%)                | 19/25 (76)            | 25/37 (67.56)         | 0.67    |

*Patients with background diseases, such as: diabetes mellitus, hypertension, hyperlipidaemia, chronic renal failure, chronic obstructive pulmonary disease (COPD), past/present oncological disease and autoimmune/rheumatic disease.

**Disease involvement, limited to mucosa only vs mucosa and skin involvement (19/25 [76%] for HSV-positive and 25/37 [67.5%] for HSV-negative).**

p-value was calculated for continuous variables using Student’s t-test, and for categorical variables using χ² test.

HSV: herpes simplex virus; PMH: past medical history; SD: standard deviation.
Comparisons of the clinical and laboratory findings between the 2 groups are summarized in Table II. Among the parameters examined, the time to first relapse was significantly shorter for patients who were HSV-positive at onset than for those who were HSV-negative (8 ± 5.6 vs 17.1 ± 8.3 months; \( p=0.0138 \)). However, the time to first relapse was not statistically significant when the Kaplan–Meier curves were compared using the log-rank test (\( p=0.15 \)), although it showed the same trend (Fig. 2). Other clinical parameters related to the disease course (e.g. number of exacerbations per year (1.6 ± 3.1 for HSV-positive vs 0.8 ± 0.6 for HSV-negative; \( p=0.13 \)) and >1 exacerbation (40% for HSV-positive vs 27.03% for HSV-negative; \( p=0.43 \)) were not statistically significant, but showed a tendency of a more severe relapsing disease in HSV-positive patients. The CRP level (38.5 ± 47.5 mg/l for HSV-positive vs 14.6 ± 17.7 mg/l for HSV-negative; \( p=0.008 \)) (Fig. 3) and PDAI score during onset (25.28 ± 8.16 for HSV-positive vs 19.03 ± 9.15 for HSV-negative; \( p=0.008 \)) were also found to be significantly higher for HSV-positive patients. Other parameters, such as the maximal prednisone dose, time to remission, number of adjuvants during exacerbation, and remission status were similar in both groups.

**DISCUSSION**

There are multiple mechanisms by which a host infection by a pathogen, such as HSV, can lead to an autoimmune burst. The most prominent theory is molecular mimicry, whereby pathogens may carry elements that are similar enough in amino acid sequence or structure to self-antigens; therefore, T or B cells, which are activated in response to the pathogen, are also cross-reactive to self and lead to direct damage. Other theories of infection-derived autoimmune bursts include viral infections that unmask autoimmune potential, viral super-antigens encoded by certain viruses, polyclonal activation, and diffusion of the epitope (8, 18, 19). According to Ruocco et al. (8), polyclonal activation occurs when lymphocytic viruses directly affect B-lymphocytes, leading to their proliferation and enhanced antibody production. Furthermore, epitope spreading is a phenomenon whereby viral infections and inflammation unmask “sequestered” self-antigens that are subsequently recognized as foreign materials and are processed by antigen-presenting cells. There is significant evidence indicating that

![Fig. 2. Kaplan–Meier curves showing time to first relapse after achieving remission for the herpes simplex virus (HSV)-positive group vs the HSV-negative group. The \( p \)-value was calculated using the log-rank test.](image1)

![Fig. 3. Beeswarm plot of C-reactive protein (CRP) values during pemphigus vulgaris (PV) onset for the herpes simplex virus (HSV)-positive group vs the HSV-negative group.](image2)

**Table II. Exacerbation severity parameters and disease course of herpes simplex-positive patients compared with herpes simplex-negative patients**

| Parameter                          | HSV-positive (\( n=25 \)) | HSV-negative (\( n=37 \)) | \( p \)-value |
|------------------------------------|--------------------------|---------------------------|---------------|
| Maximum prednisone dose, mg        | 66 ± 20.4                | 69.59 ± 22.13             | 0.52          |
| PDAI score during onset            | 25.28 ± 8.16             | 19.03 ± 9.15              | 0.008         |
| Time to remission, months          | 11.27 ± 7.46             | 10.09 ± 8.51              | 0.6           |
| Time to first relapse, months      | 8 ± 5.6                  | 17.1 ± 8.29               | 0.0138        |
| C-reactive protein, mg/l           | 38.54 ± 7.52             | 14.6 ± 17.7               | 0.008         |
| Number of adjuvants\(^a\), n (%)   | 1.4 ± 0.94               | 1.46 ± 0.72               | 0.78          |
| >1 exacerbation\(^b\), n (%)       | 10/25 (40)               | 10/37 (27.03)             | 0.43          |
| Number of exacerbations/year\(^c\)| 1.62 ± 3.08              | 0.81 ± 0.62               | 0.13          |
| First remission status\(^d\)       | 1.86 ± 0.83              | 2.09 ± 1.01               | 0.64          |

\(^a\)Number of adjuvants administered until remission. \(^b\)More than 1 pemphigus vulgaris (PV) exacerbation during follow up. \(^c\)Calculation: (number of exacerbations during follow-up)/(time of follow-up [months]/12). \(^d\)A scale based on Murrell et al. (15) 

\( * \)Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus – 1= complete remission off therapy, 2 = complete remission on therapy, 3 = partial remission off therapy, and 4 = partial remission on therapy. 

\( \pm \)Standard deviation; HSV: herpes simplex virus; PDAI: pemphigus disease activity index. Bold values denote statistical significance at the \( p<0.05 \) level.
HSV can exacerbate different autoimmune phenomena. Herpetic stromal keratitis (HSK) is caused by an HSV corneal infection, which progresses from epithelial infection to stromal keratitis. The symptoms of HSK can be alleviated using immunosuppressive drugs rather than antiviral drugs, indicating that HSK has an autoimmune component (18). Oral erythema multiforme (EM) can also be caused by autoimmune cross-reactivity from HSV infection. Immunologically, there is substantial overlap between viral and human peptides in the oral mucosa, strongly suggesting that immune cross-reactivity leads to the generation of EM (20).

Studies that had reported a relationship between HSV and PV can be classified into 3 groups: (i) studies that emphasized that viral infection is a complication of the immunosuppressive therapy; (ii) studies that claimed that HSV is a trigger with the virus being present prior to PV exacerbation; and (iii) studies that did not find any correlation between HSV and PV (21). In a study by Mohammadi et al. (11), there was a significant increase in IgG anti-HSV antibody levels found by comparing relapse and remission swab samples, suggesting an active infection during disease exacerbation. Machado et al. (12) demonstrated that the number of viral copies was reduced in uninjured areas compared with lesioned areas. However, neither study showed a causal relationship between PV and HSV. Other studies have emphasized the differences in the clinical presentation and the benefit of using antiviral therapy in PV exacerbations. Brandao et al. (9) presented a case of an upper eyelid lesion refractory to immunosuppressive therapy, which persisted for 2 months, but started to heal only after the initiation of acyclovir treatment. Konda et al. (22) demonstrated different clinical presentations with HSV-positive PV lesions compared with HSV-negative PV lesions, with the former being associated with more fissures, hemorrhagic crusts, linear erosions, and increased erythrocyte sedimentation rate (ESR).

The current study investigated the clinical and laboratory characteristics of patients with PV who were HSV-positive compared with PV patients who were HSV-negative at the time of disease onset. A male-to-female ratio of 0.55:1 was found, like the ratio reported by Konda et al. (22). Unlike Konda et al., we did not find a sex difference for HSV-positivity ($p=0.84$), but because of the relatively small group of patients, no definite conclusion can be drawn. The mean age in our study was $56.1 \pm 15.5$ years, which was consistent with the literature (2, 23).

Kurata et al. (24) showed that the mean HSV DNA copy number detected in the saliva of patients with PV was higher than with other HSV-induced disorders, such as herpes labialis and eczema herpeticum. In the current study, 25 of the 62 patients ($40.32\%$) had HSV-positive PCR results, similar to those reported by Konda et al. (22). It is worth mentioning that asymptomatic shedding of HSV could be a confounding factor in the current study results. However, according to the frequency of asymptomatic shedding reported in the literature, the rate of detection of HSV by PCR was higher in the current study; Sacks et al. (25) and Miller et al. (26) have shown a rate of HSV detection in the oral cavity of asymptomatic patients of $2.7–6.3\%$ by PCR and culture together, and Mertz et al. (27) has shown a $20\%$ asymptomatic shedding rate in anogenital sites of HSV seropositive patients. Although this issue should be considered, it is still a partial explanation of the results. Furthermore, Esmali et al. (21) and Chiu et al. (28) have raised that immunosuppressive treatment during PV exacerbation could itself predispose patients to HSV coinfection. To avoid this issue, all patients included in the study were those with PV during their first-ever exacerbation; hence, they did not receive prior immunosuppressive medication and had no immunosuppression-related conditions in their background.

The mortality rate has greatly decreased over the years because of efficient immunosuppressive treatment, the first and foremost being corticosteroids (CS), followed by CS-sparing agents, such as methotrexate, azathioprine, and rituximab (29–31). However, there are cases in which patients with PV are treated adequately, but are found to be refractory to treatment. One factor associated with treatment refractoriness is HSV coinfection (9, 24, 32, 33). The current study found that patients with PV who were HSV-positive during onset had a more severe relapsing disease course. This was supported by statistically significant findings regarding higher CRP levels ($p=0.008$), higher PDAI scores during onset ($p=0.008$) and shorter times to first relapse ($p=0.0138$). Other supporting results, despite not statistically significant, are the number of exacerbations per year ($p=0.13$) and the $>1$ exacerbation parameter ($p=0.43$). This was in accordance with other studies (22, 24, 32, 33). Kurata et al. (24) showed that HSV-positive patients were refractory to high doses of prednisone and required additional adjuvant immunosuppressive agents. Kumar et al. (32) and Kalra et al. (33) found HSV-positivity to be associated with treatment refractoriness, with the latter showing a variable extent of reduction in the size of erosions of recalcitrant lesions (10–60\%) following antiviral therapy. We believe that larger prospective trials can validate these associations with HSV-positive patients with PV.

Contrary to what we expected, the first remission status (1.86 $\pm$ 0.83 for HSV-positive vs $2.09 \pm 1.01$ for HSV-negative; $p=0.64$) and time to remission (11.3 $\pm$ 7.5 months for HSV-positive vs $10.1 \pm 8.51$ months for HSV-negative; $p=0.6$) were similar for the HSV-positive and -negative groups. In our opinion, this is explained by the fact that all HSV-positive patients in our cohort received antiviral treatment (oral acyclovir or valacyclovir) in addition to systemic corticosteroid/immunosuppressive treatment and therefore, could have achieved the...
same remission status and time to remission as the HSV-negative patients with PV who received only corticosteroid/immunosuppressive treatment. This result is supported by Konda et al. (22), who showed that the PDAI score of 23 HSV-positive patients decreased significantly (p=0.003) after 10 days of acyclovir therapy, indicating that antiviral treatment might be a critical factor in achieving an advanced remission status in HSV-positive patients. Therefore, it is reasonable to consider anti-viral therapy for HSV-positive patients to ease the severity of each flare-up. In addition, adding prophylactic antiviral treatment to reduce the number of PV flares could be a topic of interest for further studies. Unlike the remission status and time to remission following the onset of PV, other parameters, such as the time to first relapse and the number of exacerbations per year, are not influenced by antiviral therapies unless taken adequately on a permanent basis and therefore, may be associated with herpetic relapses.

This study has several limitations. First, it was a retrospective study with a relatively small number of PV cases; thus, the temporal and causal relationship between PV and HSV could not be absolutely determined. Secondly, the Sheba Medical Center and Sourasky Medical Center are tertiary referral centres that cater mostly to the severe cases of PV that are usually admitted as inpatients, whereas milder cases might be treated in the outpatient clinics; this might have affected the generalizability of the study. Finally, the HSV-status for our patients is not routinely available when they are followed at the outpatient clinic, and this point should be considered from a cost-benefit basis for future clinicians’ recommendations.

In conclusion, considering the high percentage of patients with PV who were found to be HSV-positive during onset, routine PCR tests for HSV are recommended. Furthermore, patients with PV experiencing multiple exacerbations with high CRP values and PDAI score may benefit from prophylactic antiviral treatments.

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