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ORIGINAL ARTICLE

The relationship between pemphigus and systemic lupus erythematosus: a cross-sectional study, systematic review, and meta-analysis

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Abstract

The coexistence of pemphigus and systemic lupus erythematosus (SLE) had been reported anecdotally. Anti-desmoglein (Dsg)1 and anti-Dsg3 antibodies were detected concomitantly with antinuclear autoantibodies among blood donors. The aim of the current study was to study the association between pemphigus and SLE in Israeli patients and to synthesize existing data on this association in the current literature. The current study included two sections. Initially, a cross-sectional study was performed to compare pemphigus patients with age-, sex-, and ethnicity-matched control subjects regarding the prevalence of SLE using a real-life large-scale computerized database. Next, a systematic review and meta-analysis of similar observational studies in Medline, Embase, and Web of Science (1823–2017) was conducted. As for the cross-sectional study, a total of 1985 patients with pemphigus and 9874 controls were included in the study. The prevalence of SLE was slightly higher among patients with pemphigus as compared to controls (OR, 1.85; 95% CI, 0.89–3.82). In a sensitivity analysis that included patients who received pemphigus-related treatments, the association between pemphigus and SLE had been substantiated and was statistically significant (OR, 2.10; 95% CI, 1.00–4.48). In the meta-analysis section, three eligible studies, comprising 10,389 pemphigus patients met the eligibility criteria. The overall pooled multivariate OR was 2.50 (95% CI 1.54–4.07, $I^2 = 44.19\%$, $P = 0.167$) across all studies. In conclusion, the meta-analysis provides epidemiologic evidence that these B cell-driven diseases are significantly associated. Further research is required to elucidate the molecular mechanism underlying this association.

Keywords Pemphigus · SLE · Systemic lupus erythematosus · Lupus · Association · Meta-analysis · Systematic review

Introduction

The simultaneous occurrence of pemphigus and systemic lupus erythematosus (SLE) has been reported in several individuals [1]. However, observational studies aiming to investigate the association between these two antibody-mediated diseases are scarce and inconclusive [2–4]. A large-scale serological study among healthy blood donors revealed concomitant detection of anti-Dsg1 and anti-Dsg3 with antinuclear autoantibodies (ANA), the main immunological hallmark of SLE [5, 6]. A recent in silico study revealed novel mutual candidate genetic markers and pathways in $CD4^+$ T cells that are shared between pemphigus and SLE [7].

The primary endpoint of the current study is to further define the association between pemphigus and SLE using a

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large-scale population-based study. Additionally, we performed a systematic review and meta-analysis with the aim to synthesize the current data from previous observational studies about the relationship between these two conditions.

Methods

Cross-sectional study section

We utilized the Clalit Healthcare Services (CHS) database of health information collected between the years 2004 and 2014 to conduct this population-based cross-sectional study. Further information regarding the dataset is elaborated in our previous publications [8–10]. Patients were defined as having both pemphigus and SLE when at least two documented diagnoses of these entities were registered in their medical records by a physician in the community, or when both pemphigus and SLE were in the listed diagnoses within discharge letters from a hospital. Up to five control patients were randomly selected for each case patient. The case and control groups were frequency-matched in terms of sex, age, and ethnicity. This study was approved by the institutional ethical board of Ben-Gurion University and by CHS.

We compared the distribution of sociodemographic and clinical variables between patients with and without pemphigus using Chi-square and Student *t* tests. We compared the prevalence of SLE between the study groups in the entire study sample as well as in the age and sex subgroups. Crude odds ratio (OR) as well as 95% confidence interval (CI) are presented. A logistic regression model was used to estimate the association between pemphigus and SLE in a multivariate analysis. All statistical analyses were performed using the SPSS software, version 23 (SPSS, Chicago, IL, USA).

Systematic review and meta-analysis section

The literature review was conducted using Ovid-Medline (1946–present), Embase (1947–present), and Web of Science (1900–present) to identify eligible studies. Publications up to May 3, 2018 were searched independently and cross-checked by two researchers. The search strategies are detailed in the Supplementary Table 1. Reference lists of included studies were further screened for additional eligible publications.

Studies were excluded based on the title and/or abstract if there was no clear indication that they investigated the association of pemphigus with SLE. Reviews, case series, and uncontrolled observational studies lacking ORs were all excluded. Two researchers independently performed data extraction from included studies, and any differences were resolved by discussion. Each paper was critically reviewed for the

Table 1 Descriptive characteristics of the study participants

Characteristic	Patients with pemphigus (*N* = 1985)	Controls (*N* = 9874)	*P* value
Age, years			
Mean ± SD	72.1 ± 18.5	72.1 ± 18.5	1.000
Median (range)	77.4 (0–103.0)	77.4 (0–103.1)	
Male sex, *N* (%)	797 (40.2%)	3962 (40.1%)	0.934
Ethnicity, *N* (%)			
Jews	1805 (90.9%)	8866 (89.8%)	0.136
Arabs	180 (9.1%)	1008 (10.2%)	
BMI, kg/m^2 (Mean ± SD)	27.7 ± 6.6	27.9 ± 6.6	0.355
Smoking, *N* (%)	510 (25.7%)	2758 (27.9%)	0.045
SES, *N* (%)			
Low	634 (31.9%)	3249 (32.9%)	0.386
Intermediate	830 (41.8%)	4263 (43.2%)	0.250
High	423 (21.3%)	2217 (22.5%)	0.241
Charlson comorbidity score, *n* (%)			
None (0)	344 (17.3%)	2636 (26.7%)	< 0.001
Moderate (1–2)	582 (29.3%)	3183 (32.2%)	0.011
Severe (≥ 3)	1059 (53.4%)	4055 (41.1%)	< 0.001
Healthcare utilization, *n* (%)			
0 visits	286 (14.4%)	770 (7.8%)	< 0.001
1–12 visits	411 (20.7%)	2094 (21.2%)	0.248
≥ 13 visits	1288 (64.9%)	7010 (71.0%)	< 0.001

N, number; *SD*, standard deviation; *BMI*, body mass index; *SES*, socioeconomic status

crude OR, multivariate OR, and 95% CI for ORs. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis was used [11]. High-quality studies were defined as a score of at least 6 out of 9 total points on the NOS. Egger test and funnel plot were used to assess for potential publication bias.

The overall pooled estimate and 95% CI were obtained using either a fixed (inverse variance methods) or random (DerSimonian and Laird) effects meta-analysis model, depending on the heterogeneity. Significant heterogeneity of results was detected across studies using a Cochrane Q statistic P value less than 0.05, I^2 statistic greater than 50%, or both. A 2-sided P value of 0.05 was considered to be significant. Statistical analyses were conducted using a Comprehensive Meta-Analysis software (version 3.3, 2014), Englewood, NJ, USA.

Results

Cross-sectional study section

Our study included a total of 1985 patients diagnosed with pemphigus between 2004 and 2014 and 9874 age-, sex-, and ethnicity-matched control subjects. The mean (± SD) age at presentation of pemphigus was 72.1 ± 18.5 years, which is identical to the age of enrollment of controls. In all, 797 (40.2%) of cases were male, with a similar proportion seen in controls. Ethnicity and socioeconomic status of the two groups were also similar. Comorbidity rates, as measured by the Charlson index, were higher in cases, with 1059 (53.4%) patients affected by severe comorbidity relative to 4055 (41.1%) control subjects ($P < 0.001$; Table 1).

The prevalence of SLE was slightly higher among patients with pemphigus (0.5%) as compared to controls (0.3%), although it did not exceed the conventional level of statistical significance (OR, 1.85; 95% CI, 0.89–3.82). Table 2 summarizes ORs for SLE in patients with pemphigus and controls across the entire study sample, as well as across stratifications by age, sex, ethnicity, and smoking status. The association of SLE and pemphigus was statistically significant among patients aged between 40 and 60 years but was inconclusive in the remaining age categories, in both sexes, and regardless of the smoking status (Table 2).

We performed a sensitivity analysis that included only pemphigus patients prescribed one of the following "pemphigus-related treatments": systemic corticosteroids, adjuvant immunosuppressive agents (azathioprine, mycophenolate mofetil, cyclophosphamide), or one or more cycles of rituximab. In our analysis, the association between pemphigus and SLE was confirmed and exceeded the level of statistical significance (OR, 2.10; 95% CI, 1.00–4.48; Table 2). In a multivariate logistic regression model, no association was

Table 2 The association between pemphigus and SLE stratified by age, sex, and ethnicity

Subgroup	Number	SLE in patients with pemphigus ($N = 1985$) N (%)	SLE in controls ($N = 9874$) N (%)	OR (95% CI)	Univariate P value	Sensitivity analysis OR (95% CI)*	Sensitivity analysis P value	Multivariate OR**	Multivariate P value
All	11,859	10 (0.5%)	27 (0.3%)	1.85 (0.89–3.82)	0.093	*2.10 (1.00–4.48)*	*0.049*	1.52 (0.73–3.16)	0.263
Age, years									
0–39	872	0 (0.0%)	2 (0.3%)	0.99 (0.99–1.00)	0.529	0.99 (0.99–1.00)	0.582	NA	NA
40–59	1768	3 (1.0%)	3 (0.2%)	*5.03 (1.01–25.07)*	*0.028*	*6.00 (1.20–29.89)*	*0.013*	3.85 (0.63–23.61)	0.146
≥60	9219	7 (0.5%)	22 (0.3%)	1.58 (0.68–3.71)	0.287	1.73 (0.69–4.27)	0.230	1.28 (0.51–3.21)	0.593
Sex									
Male	4759	2 (0.3%)	5 (0.1%)	1.99 (0.39–10.28)	0.402	2.59 (0.50–13.38)	0.238	1.52 (0.28–8.32)	0.631
Female	7100	8 (0.7%)	22 (0.4%)	1.82 (0.81–4.09)	0.144	1.97 (0.84–4.63)	0.112	1.47 (0.62–3.48)	0.384
Smoking status									
Smokers	3267	3 (0.6%)	5 (0.2)	3.26 (0.78–13.67)	0.088	4.02 (0.98–16.87)	*0.040*	2.33 (0.54–9.97)	0.257
Non-smokers	8592	7 (0.5%)	22 (0.3%)	1.54 (0.66–3.61)	0.319	1.68 (0.68–4.15)	0.255	1.20 (0.51–2.84)	0.677

SLE, systemic lupus erythematosus; *OR* odds ratio; *N*, number; *CI*, confidence interval; *NA*, not applicable

Italics: significant value

*Sensitivity analysis included only pemphigus patients under prolonged "pemphigus-related treatments"

**Adjusted for healthcare utilization and Charlson score

observed between pemphigus and SLE (OR, 1.52; 95% CI, 0.73–3.16; $P = 0.263$) after adjusting for comorbidities and overutilization of healthcare services (Table 2).

Systematic review and meta-analysis section

The literature search yielded 612 manuscripts. Five additional articles were identified via other sources. Four hundred and fourteen articles were duplicates, and 188 were unrelated to the association between pemphigus and SLE. Full-text review was performed on the remaining 15 articles. Overall, two studies fulfilled the eligibility criteria and were included in the quantitative synthesis [3, 4]. The current cross-sectional study met the eligibility criteria and was therefore included in the quantitative synthesis. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram is demonstrated in Fig. 1.

The three eligible studies comprised a total of 10,389 pemphigus patients from three different countries, encompassing participants of all ages, both males and females. Study publication dates ranged from the years 2016 to 2018, and follow-up periods covered the years 1997–2014. The mean age of patients with pemphigus in the different study cohorts ranged between 58.0 in Taiwan [3] and 72.1 years in Israel. Quality assessment using the NOS scale revealed that two of the three included studies had scores of six or greater. The studies' characteristics are described in Table 3.

Multivariate ORs for SLE among patients with pemphigus ranged from 1.52 (95% CI, 0.73–3.16) in Israel to 4.46 (95% CI, 1.88–10.60) in Taiwan [3]. The pooled multivariate OR was 2.50 (95% CI, 1.54–4.07; $I^2 = 44.19\%$; $P = 0.167$) across all studies (Fig. 2). In a sensitivity analysis excluding the study with low NOS [4], the pooled OR did not change substantially (OR, 2.54; 95% CI, 0.89–7.28; $I^2 = 95.0\%$; $P < 0.001$).

Publication bias was not identified, as seen by the nonsignificant result of the Egger test for asymmetry of funnel plot regression for the main outcome of the study ($P = 0.300$; Supplementary Fig. 1).

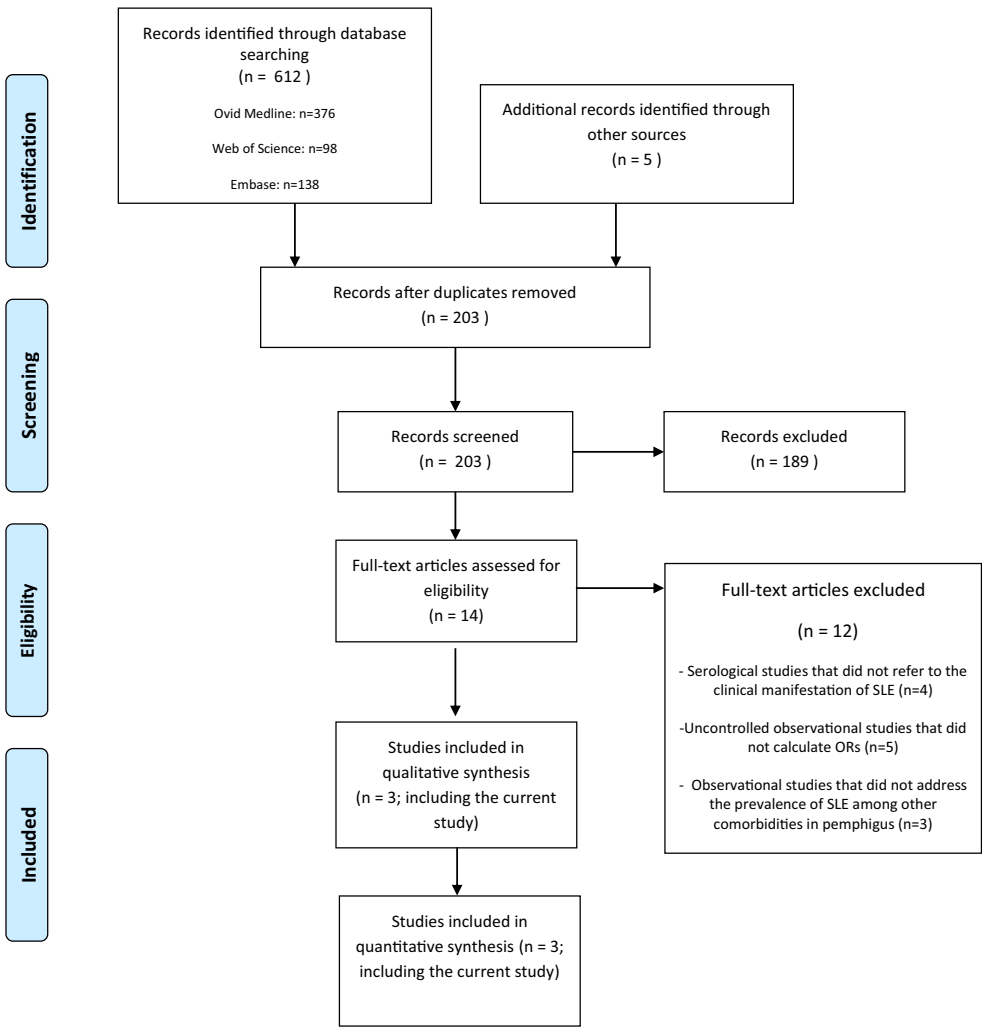

Fig. 1 PRISMA flow diagram of literature search and study selection for meta-analysis

Table 3 Characteristics of studies which evaluated the association between pemphigus and SLE

Study	Design	Location	Period	Number of patients	Number of control subjects	Average age, years	% female patients	Crude OR	Multivariate OR	NOS
Hsu et al. [4], 2016	Cross-sectional	USA	2002–2012	6406	87,033,305	68.2	59.1	1.52 (0.63–3.65)	2.91[1] (1.08–7.82)	3
Chiu et al. [3], 2017	Cross-sectional	Taiwan	1997–2010	1998	7992	58.0*	47.7	5.24 (2.29–12.0)	4.46[2] (1.88–10.6)	6
Kridin et al., 2018 (the current study)	Cross-sectional	Israel	2004–2014	1985	9874	72.4	59.8	1.85 (0.89–3.82)	1.52 (0.73–3.16)	7

N, number; *OR*, odds ratio; *CI*, confidence interval; *NOS*, Newcastle-Ottawa scale

*Median age

[1] Adjusted for age, sex, other comorbid diseases visit times, annual income, and area

[2] Adjusted for age, sex, and race

Discussion

The current large-scale cross-sectional study reveals that the association between pemphigus and SLE in Israeli patients fell narrowly short of significance (OR, 1.85; 95% CI, 0.89–3.82). To our knowledge, we have performed the first systematic review and meta-analysis synthesizing data across controlled observational studies that examine the relationship between these two antibody-mediated diseases. This quantitative synthesis showed that pemphigus and SLE are significantly associated (pooled OR, 2.50; 95% CI, 1.54–4.07).

"The Autoimmune Diathesis" is an acceptable concept claiming that individuals affected by an autoimmune disease are more predisposed to suffer from other simultaneous autoimmune disease [12–14]. Based on previous observational studies, pemphigus was found to be associated with other autoimmune diseases, including rheumatoid arthritis [2, 15], autoimmune thyroid diseases [2, 15], type I diabetes mellitus [2], Sjögren's syndrome [3], alopecia areata [3], ulcerative colitis [16], and myasthenia gravis [4]. Similarly, SLE was reported to cluster with a wide range of autoimmune disorders, with one study reporting that 30% of SLE patients had at least one other autoimmune disease [17].

In 2007, Malik and Ahmed [1] reviewed the literature and summarized eight cases with a definitive dual diagnosis of SLE and pemphigus; seven of them presented with pemphigus vulgaris, whereas the remaining patient had pemphigus erythematosus. The course of the two diseases among these patients appeared unrelated, while the demographic profile was more typical of SLE than of pemphigus vulgaris. In their cluster analysis, Parameswaran et al. [2] identified a distinct autoimmune cluster linking pemphigus vulgaris with SLE, autoimmune thyroid diseases, and rheumatoid arthritis. This study was not included in the quantitative synthesis since it did not comprise a matched control group [2].

The findings of the meta-analysis are reinforced by serological studies demonstrating that patients with pemphigus vulgaris more frequently test positive for non-organ-specific autoantibodies, including ANA [18, 19]. Actually, ANA was detected in approximately one third of patients with pemphigus vulgaris, leading some authors to advocate for screening for signs and symptoms of connective tissue disease in these patients [18, 19]. Moreover, the most commonly recognized staining pattern of ANA on indirect immunofluorescence among pemphigus patients was the homogeneous pattern, which is more implicated with active SLE [18]. The co-occurrence of Dsg1 and Dsg3 with SLE-associated ANA in a study of 6000 healthy blood donors may indicate a shared control of the production of these autoantibodies [6]. The recently identified molecular mechanisms and pathways between pemphigus and SLE may also lend credibility to the findings of our pooled analysis [7].

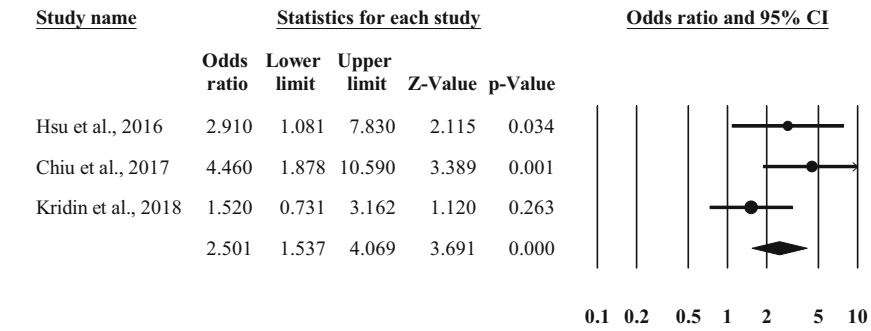

Fig. 2 Forest plot summarizing the OR for SLE in patients with pemphigus. The OR of the individual studies is represented by cycles, through which the horizontal lines represent the 95% CIs. The diamond at the bottom represents the pooled OR of these studies

The molecular mechanism underlying this association has yet to be elucidated. However, the coexistence of pemphigus and SLE may provide a novel opportunity to study if targeted therapies that remove the B lymphocyte clones that generate autoantibodies are associated with either disease or with both [1]. It is well established that both patients with pemphigus and SLE often show autoantibodies to several antigens, implying that epitope-spreading phenomenon might play a part in the pathogenesis [20, 21]. In this concept, an inflammatory event exposes new target antigens to the immune system, thus inducing a subsequent autoimmune response to new antigens [22]. Further research is necessary to glimpse through the pathomechanism by which these conditions are interrelated.

The cross-sectional study limitations include a lack of data concerning the immunopathological subtype, clinical features, and severity of the diseases. The utilization of routinely collected data interferes with a direct validation of diagnoses; however, it is improbable that significant misclassification meaningfully interfered with our findings. To counter such misclassification, we performed a sensitivity analysis to validate the diagnosis of pemphigus among cases. The meta-analysis may be limited by the fact that all included studies were retrospective and observational, with several methodological limitations, and that the pooled studies had different sample sizes and geographic locations. However, the low heterogeneity across most comparisons increases its validity.

In conclusion, although the association of pemphigus and SLE was of only marginal statistical significance among Israeli patients in the current cross-sectional study, the subsequent meta-analysis indicates that these B cell-driven diseases are significantly associated. Given the epidemiological, serological, and genetic evidence, clinicians caring for patients with pemphigus should be aware of this association.

Compliance with ethical standards

Conflict of interests Prof. Arnon Cohen received research grants from Janssen, Novartis, AbbVie, Janssen, and Sanofi. Prof. Arnon Cohen served as a consultant, advisor, or speaker to AbbVie, Amgen, Boehringer Ingelheim, Dexcel pharma, Janssen, Kamedis, Lilly, Neopharm, Novartis, Perrigo, Pfizer, Rafa, Samsung Bioepis, Sanofi, Sirbal, and Taro. No funding was gained for the research.

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