Association of pemphigus and systemic corticosteroid use with comorbid health disorders: A case-control study

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Abstract

Background: Pemphigus is a group of debilitating autoimmune blistering disorders associated with painful blisters of the skin and/or mucous membranes. Identification and management of the comorbidities of pemphigus is critically important to minimize morbidity and decrease mortality.

Objective: To identify the comorbid health conditions of pemphigus vulgaris.

Methods: This was a case-control study of 130 cases of pemphigus verified by a clinical and laboratory diagnosis and 390 age and sex-matched controls with complete follow-up at a large metropolitan quaternary care medical center.

Results: Pemphigus vulgaris and its treatments were significantly associated with type 2 diabetes mellitus (adjusted odds ratio [95% confidence interval]: 5.68 [2.93-11.02]), hypertension (2.15 [1.25-3.71]), osteopenia (10.07 [3.72-27.25]), osteoporosis (4.19 [1.50-11.73]), cataracts (7.00 [1.81-27.07]), insomnia (15.00 [1.75-128.39]), and benign prostatic hyperplasia (6.84 [1.79-26.18]). A history of taking systemic corticosteroids was found in 76% of pemphigus vulgaris patients. There were significant statistical interactions between pemphigus vulgaris and a history of using systemic corticosteroids as predictors of diabetes mellitus type 2, hypertension, osteoporosis, and insomnia.

Conclusions: Safer and more effective systemic treatment options are needed for pemphigus to minimize iatrogenic complications of disease.

Keywords: pemphigus, comorbidities, epidemiology, corticosteroids, infection, immunosuppressants, cardiovascular, mental health

Introduction

Pemphigus is a group of debilitating autoimmune blistering disorders associated with painful blisters of the skin and/or mucous membranes. The disease is characterized by autoantibodies attacking epidermal antigens resulting in acantholytic blisters. Pemphigus is associated with substantial morbidity secondary to skin and mucosal disease as well a number of comorbid health disorders. Identification and management of the comorbidities of pemphigus is critically important to minimize morbidity and decrease mortality.

In various cohort studies and case reports, pemphigus has been associated with cardiovascular disease risk factors, such as type 2 diabetes mellitus and hyperlipidemia, infections, various autoimmune diseases, decreased bone mineral density and adrenal insufficiency, malignancies, and psychiatric comorbidities [1-5]. However, the comorbidities of pemphigus in relation to subtype, disease severity, and medication history have not been well-described. In the present study, we sought to determine the major health comorbidities of adults with pemphigus.

Methods

Subjects and matching

The study was approved by the institutional review board for human subjects of Northwestern Medicine, Chicago, IL. All patients with pemphigus

(International Classification of Disease 9th revision clinical modification diagnosis code: 694.4) and a random sample of age and sex-controlled non-pemphigus controls were selected from the Northwestern Medicine Electronic Data Warehouse, which includes the medical records of > 2.5 million individuals across a large quaternary care hospital and outpatient network. Electronic medical records were reviewed in their entirety in both outpatient and inpatient settings. Cases with a diagnosis of pemphigus between January 2001 and November 2014 were included in this study. Inclusion criteria were adults aged 18-89 years, male or female, who received care in the Northwestern Medicine network. Exclusion criteria included inadequate documentation to support a diagnosis of pemphigus (cases) and incomplete follow-up (cases and controls). Controls were pair-wise matched by age in years and sex, with 3 controls per case. Cases and controls were linked by a blocking variable that was used for conditional logistic regression.

Data collection

Subjects with pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus, and drug-induced pemphigus were identified. The diagnosis of pemphigus was confirmed by the presence of a clinical diagnosis by a board-certified dermatologist and at least one of the following documented: perilesional biopsy with direct immunofluorescence staining, serum collection with indirect immunofluorescence staining, and/or enzyme-linked immunosorbent assay consistent with pemphigus. Severity of pemphigus was classified by a dermatologist as mild, moderate, or severe based on lesion extent and quality of life impairment without the usage of an established scoring system. In addition to clinical and laboratory documentation of pemphigus, other data collected from the electronic medical record included: race/ethnicity, specific type of pemphigus, age of diagnosis of pemphigus, presence of any comorbid health conditions, medication history, and duration of corticosteroid usage (months).

Sample Size Calculation

Sample size calculation was based on the outcome type 2 diabetes mellitus. A priori power analysis was based on the Fisher exact test assuming 85 percent power, with the use of two-sided tests and an alpha level of 0.01. The non-exposure rate in the control or "referent" group was predicted to be 87.7%, based on recent data demonstrating a 12.3% prevalence of type 2 diabetes mellitus in adults in the United States [6]. The odds ratio of developing type 2 diabetes mellitus in pemphigus was predicted to be 2.0. With 3:1 control matching, the number of patients needed was estimated to be 194, with approximately 49 pemphigus cases and 147 controls. However, we oversampled for both cases and controls in order to increase powering for rare outcomes.

Data Processing and Statistical Methods

The baseline characteristics of those patients with pemphigus and those without were examined. Conditional logistic regression for matched analysis was used to determine whether pemphigus was associated with other health comorbidities. Since matching was performed by age and sex, models were stratified by a blocking variable that represented age- and sex-matched pairs. Since subjects were matched by current age (age on November 13th, 2015) and sex, current age (continuous) and sex (binary) were included as covariates in all models. Adjusted odds ratio and 95% confidence interval were estimated. Additional matching by other demographic variables was not performed as it was deemed to decrease statistical efficiency, not eliminate confounding from other variables and even introduce unnecessary bias into the study design.

Sensitivity analyses were performed to determine whether any significant associations between pemphigus vulgaris and comorbidities were related to pemphigus vulgaris severity or use of systemic corticosteroids. In the former models, pemphigus vulgaris severity (mild or moderate/severe versus none) was the independent variable. In the latter models, pemphigus vulgaris (yes versus no), history of systemic corticosteroid usage (yes versus no) and a two-way interaction term between them were the independent variables. Significant interactions were judged by an interaction term P-value <0.05 and ≥20% increase in the odds ratio between pemphigus vulgaris patients with and without corticosteroid usage. All models controlled for age and sex.

All data analyses and statistical processes were

Table 1. Patient demographics.			
Variable	**No Pemphigus (n = 390)**	**Pemphigus (n = 130)**	**P-value**
Age - mean (SD)	59.2 (14.1)	59.2 (14.4)	NA
Female - Freq (%)	204 (52.3%)	68 (52.3%)	NA
Race - Freq (%)			
White	185 (76.1%)	76 (58.5%)	-
Black	28 (11.5%)	13 (10.0%)	0.6
Hispanic	16 (6.6%)	23 (17.7%)	0.004
Asian	14 (5.8%)	18 (13.9%)	0.002

performed using SAS version 9.4 (SAS Institute, Cary, NC). Post-hoc correction for multiple dependent tests was performed by minimizing the false discovery rate with the approach of Benjamini and Hochberg [7] and corrected P-values are presented. Two-sided corrected P-values less than or equal to 0.05 were considered significant.

Results

Population characteristics

Two hundred sixty-six patients were identified using the International Classification of Disease 9th revision clinical modification code 694.4; 136 were excluded based on exclusion criteria. Of the 130 pemphigus patients included, 102 were classified with pemphigus vulgaris, 19 with pemphigus foliaceus, 3 with familial benign pemphigus, 4 with pemphigus vegetans, and 1 with pemphigus erythematosus. Three hundred ninety age- and sex-matched patients without a history of pemphigus, who had complete follow-up and met exclusion criteria, were randomly selected as controls. Conditional logistic regression models were constructed using the blocking variable based on age and sex matching. Therefore, age and sex were included as a covariate in all final models. Both cohorts consisted of 52.3% females and mean age of 59.2 years. Pemphigus patients compared with controls were more likely to be Hispanic (17.7% versus 6.6%) and Asian (13.9% versus 5.8%) and less likely to be white (58.5% versus 76.1%), P = 0.004, **Table 1**.

Pemphigus patients were diagnosed at a median age of 48.5 years (interquartile range: 18.5). Forty-nine pemphigus patients had mild, 31 moderate, and 34 severe disease based on physician assessment. Forty-one (31.5%) of the pemphigus cohort had a history of inpatient hospitalization for any reason. In our patient population, 14 (10.8%) of patients were hospitalized for pemphigus. No patients died during the hospital stay.

Of the 102 pemphigus vulgaris patients, systemic drug history revealed the use of mycophenolate mofetil in 38 (37.3%), rituximab in 12 (11.8%), cyclosporine in 1 (1.0%), methotrexate in 5 (4.9%), azathioprine in 17 (16.7%), and cyclophosphamide in 18 (17.7%), **Table 2**. Thirty-two (31.4%) patients had no history of usage of systemic agents and 50 (49.0%) had a history of usage of only one systemic agent. Furthermore, 17 (16.7%) had used two systemic agents and 3 (2.9%) had used three agents. Seventy-seven (75.5%) patients had a history of systemic corticosteroid usage, with a mean ± standard deviation months of usage of 20.3 (31.8) months. Of 40 pemphigus vulgaris patients classified with a "mild" clinical diagnosis, 26 (65.0%) had a history of systemic corticosteroid usage. However, of 48 patients classified with a "moderate" or "severe"

Table 2. Medication profile of pemphigus vulgaris patients.	
Variable	**Freq (%)**
Systemic agents	
Mycophenolate mofetil	38 (37.3%)
Rituximab	12 (11.8%)
Cyclosporine	1 (1.0%)
Methotrexate	5 (4.9%)
Azathioprine	17 (16.7%)
Cyclophosphamide	18 (17.7%)
Systemic steroids	77 (75.5%)
No. of months of steroid use – mean (SD)	20.3 (31.8)
Number of systemic agents	
0	32 (31.4%)
1	50 (49.0%)
2	17 (16.7%)
3	3 (2.9%)

clinical severity, 44 (91.7%) had a history of systemic corticosteroid usage.

Comorbidities of pemphigus

Of 47 comorbidities surveyed, 8 were significantly associated with pemphigus. The associated comorbid health conditions included diabetes mellitus type 2 (adjusted odds ratio [95% confidence interval]: 4.39 [2.52-7.91]), hypertension (2.08 [1.28-3.40]), osteopenia (6.69 [2.92-15.35]), osteoporosis (5.46 [2.20-13.57]), cataracts (4.47 [1.45-13.78]), anxiety (2.89 [1.33-6.25]), insomnia (18.00 [2.17-149.51]), and benign prostatic hyperplasia (7.82 [2.09-29.26]), **Table 2**. In sensitivity analysis of pemphigus vulgaris patients per se, 7 comorbidities remained significantly associated: type 2 diabetes mellitus (5.68 [2.93-11.02]), hypertension (2.15 [1.25-3.71]), osteopenia (10.07 [3.72-27.25]), osteoporosis (4.19 [1.50-11.73]), cataracts (7.00 [1.81-27.07]), insomnia (15.00 [1.75-128.39]), and benign prostatic hyperplasia (6.84 [1.79-26.18]), **Table 3**.

Among pemphigus vulgaris patients who were classified as having "mild" pemphigus per clinical assessment, three comorbidities remained significantly associated: diabetes mellitus type 2 (3.48 [1.31-9.26]), osteopenia (11.08 [2.34-52.58]), and cataracts (6.00 [1.10-32.76]), **Table 4**. However, among pemphigus vulgaris patients with "moderate" or "severe" disease, six comorbidities remained significantly associated: diabetes mellitus type 2 (7.15 [3.16-16.21]), hypertension (2.87 [1.44-5.73]),

Table 3. Comorbidities of patients with pemphigus.

Comorbidity	Pemphigus						
	None	Any type			Vulgaris (PV)		
	Freq (%)	Freq (%)	Adj OR (95% CI)	P	Freq (%)	Adj OR (95% CI)	P
Type 2 diabetes mellitus	30 (7.7%)	34 (26.4%)	**4.46 (2.52-7.91)**	**0.002**	30 (29.7%)	**5.68 (2.93-11.02)**	**0.002**
Hypertension	102 (26.2%)	52 (40.0%)	**2.08 (1.28-3.40)**	**0.02**	42 (41.2%)	**2.15 (1.25-3.71)**	**0.03**
Hyperlipidemia	91 (23.3%)	38 (29.2%)	1.39 (0.86-2.25)	0.4	30 (29.4%)	1.39 (0.80-2.39)	0.6
Obesity	22 (5.6%)	13 (10.0%)	1.97 (0.95-4.07)	0.2	8 (7.8%)	1.75 (0.72-4.24)	0.5
Stroke	10 (2.6%)	3 (2.3%)	1.00 (0.26-3.84)	0.9	2 (2.0%)	0.75 (0.16-3.53)	0.8
Myocardial infarction	10 (2.6%)	3 (2.3%)	0.90 (0.25-3.27)	0.9	3 (2.9%)	0.90 (0.25-3.27)	0.9
CAD	32 (8.2%)	12 (9.2%)	1.16 (0.55-2.42)	0.8	10 (9.8%)	1.24 (0.56-2.78)	0.8
CHF	9 (2.3%)	6 (4.7%)	2.30 (0.72-7.36)	0.4	4 (4.0%)	1.79 (0.50-6.44)	0.6
Atrial fibrillation	18 (4.6%)	3 (2.3%)	0.47 (0.13-1.68)	0.4	2 (2.0%)	0.43 (0.10-1.89)	0.5
Any malignancy	43 (11.0%)	12 (9.2%)	0.75 (0.36-1.53)	0.7	9 (8.8%)	0.62 (0.27-1.40)	0.5
CLL	2 (0.5%)	1 (0.8%)			1 (1.0%)		
Oropharyngeal cancer	3 (0.8%)	1 (0.8%)			1 (1.0%)		
Breast cancer	13 (3.3%)	3 (2.3%)			2 (2.0%)		
SCC of skin	6 (1.5%)	1 (0.8%)			1 (1.0%)		
BCC of skin	14 (3.6%)	2 (1.5%)			2 (2.0%)		
Prostate cancer	12 (3.1%)	4 (3.1%)			2 (2.0%)		
Bladder cancer	3 (0.8%)	2 (1.5%)			2 (2.0%)		
Gastric cancer	-	1 (0.8%)			1 (1.0%)		

Table 3. Comorbidities of patients with pemphigus.

Lung cancer	4 (1.0%)	1 (0.8%)			1 (1.0%)		
Ovarian cancer	1 (0.3%)	1 (0.8%)			1 (1.0%)		
Bone fracture	9 (2.3%)	4 (3.1%)	1.48 (0.43-5.15)	0.8	4 (3.9%)	2.03 (0.54-7.72)	0.5
Osteopenia	10 (2.6%)	19 (14.6%)	**6.69 (2.92-15.35)**	**0.002**	18 (17.6%)	**10.07 (3.72-27.25)**	**0.002**
Osteoporosis	11 (2.8%)	16 (12.3%)	**5.46 (2.20-13.57)**	**0.003**	11 (10.8%)	**4.19 (1.50-11.73)**	**0.03**
Osteoarthritis	28 (7.2%)	8 (6.2%)	0.92 (0.40-2.10)	0.9	5 (4.9%)	0.69 (0.25-1.91)	0.7
Gout	5 (1.3%)	1 (0.8%)			1 (1.0%)		
Cataracts	6 (1.5%)	9 (6.9%)	**4.47 (1.45-13.78)**	**0.04**	8 (7.8%)	**7.00 (1.81-27.07)**	**0.03**
Glaucoma	9 (2.3%)	4 (3.1%)	1.36 (0.40-4.57)	0.8	4 (3.9%)	2.13 (0.56-8.08)	0.5
Adrenal insufficiency	-	1 (0.8%)			-		
Cushing syndrome	-	1 (0.8%)			1 (1.0%)		
Hypothyroidism	31 (8.0%)	12 (9.2%)	1.15 (0.56-2.38)	0.8	9 (8.8%)	1.16 (0.50-2.69)	0.8
Multiple sclerosis	2 (0.5%)	1 (0.8%)			-		
Hyperparathyroidism	1 (0.3%)	3 (2.3%)	9.00 (0.94-86.52)	0.2	2 (2.0%)	6.00 (0.54-66.17)	0.3
Rheumatoid arthritis	2 (0.5%)	1 (0.8%)			1 (1.0%)		
Migraine	13 (3.3%)	4 (3.1%)	1.09 (0.35-3.43)	0.9	4 (3.9%)	1.33 (0.41-4.33)	0.8
Anxiety	15 (3.8%)	14 (10.8%)	**2.89 (1.33-6.25)**	**0.03**	11 (10.8%)	2.60 (1.10 -6.15)	0.1
Depression	29 (7.4%)	17 (13.1%)	1.77 (0.94-3.33)	0.2	13 (12.7%)	1.47 (0.72-3.01)	0.5
Fibromyalgia	5 (1.3%)	1 (0.8%)			1 (1.0%)		
Insomnia	2 (0.5%)	6 (4.6%)	**18.00 (2.17-149.51)**	**0.04**	5 (4.9%)	**15.00 (1.75-128.39)**	**0.04**
Obstructive sleep apnea	16 (4.1%)	4 (3.1%)	0.72 (0.23-2.22)	0.8	3 (2.9%)	0.78 (0.20-2.94)	0.8
Seizure	10 (2.6%)	2 (1.5%)	0.60 (0.13-2.74)	0.8	2 (2.0%)	0.86 (0.18-4.13)	0.9
Chronic kidney disease	5 (1.3%)	2 (1.5%)			2 (2.0%)		
ESRD	3 (0.8%)	1 (0.8%)			0 (0.0%)		
Nephrolithiasis	15 (3.8%)	3 (2.3%)	0.45 (0.10-1.99)	0.5	3 (2.9%)	0.53 (0.12-2.38)	0.6
BPH	6 (1.5%)	9 (6.9%)	**7.82 (2.09-29.26)**	**0.04**	8 (7.8%)	**6.84 (1.79-26.18)**	**0.03**
Asthma	21 (5.4%)	7 (5.4%)	0.85 (0.34-2.14)	0.8	5 (4.9%)	0.79 (0.26-2.43)	0.8
COPD	9 (2.3%)	3 (2.3%)	0.67 (0.14-3.09)	0.8	3 (2.9%)	1.00 (0.20-4.96)	1.0
Pulmonary embolism	3 (0.8%)	4 (3.1%)	6.00 (1.10-32.76)	0.1	3 (2.9%)	4.50 (0.75-26.93)	0.3

CAD, coronary artery disease; CHF. congestive heart failure; CLL, chronic lymphocytic leukemia; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; ESRD, end-stage renal disease; BPH, benign prostatic hyperplasia; COPD, chronic obstructive pulmonary disease.

Multivariate conditional logistic regression models were constructed with each comorbidity as the binary dependent variable. The independent variables were any type of pemphigus or pemphigus vulgaris, as well as age and sex. Post-hoc correction for multiple dependent tests was performed by minimizing the false discovery rate with the approach of Benjamini and Hochberg [7]. Corrected P-values are presented.

osteopenia (8.55 [2.75-26.63]), osteoporosis (6.00 [1.81-19.93]), insomnia (12.00 [1.34-107.37]), and benign prostatic hyperplasia (4.56 [1.05-18.95]), **Table 4**.

There were significant statistical interactions between pemphigus vulgaris and history of using systemic corticosteroids as predictors of diabetes mellitus type 2, hypertension, osteoporosis, and insomnia (P<0.006 for all), **Table 5**. Pemphigus vulgaris without any history of systemic corticosteroid use was associated with significantly higher odds of type 2 diabetes mellitus (adjusted odds ratio [95% confidence interval]: 3.71 [1.40-9.84]). However, pemphigus vulgaris patients with a history of systemic corticosteroid use had even higher odds of diabetes mellitus type 2 (5.85 [3.05-11.19]). Nevertheless, pemphigus vulgaris was only associated with hypertension (2.81 [1.61-4.90]), osteoporosis (7.33 [2.93-18.06]), and insomnia (10.95 [2.00-59.67]) in those with a history of systemic corticosteroid usage. There were no other significant interactions between pemphigus vulgaris and systemic corticosteroid usage as predictors of other comorbidities.

Discussion

In the present study, pemphigus and its treatments were associated with numerous comorbid health conditions. In particular, pemphigus vulgaris was associated with diabetes mellitus type 2, hypertension, osteopenia, osteoporosis, cataracts, insomnia, and benign prostatic hypertrophy. Mild pemphigus vulgaris was associated with diabetes mellitus type 2, osteopenia, and cataracts, whereas moderate-severe pemphigus vulgaris was associated with diabetes mellitus type 2, hypertension, osteopenia, osteoporosis, insomnia, and benign prostatic hypertrophy. The association between pemphigus vulgaris and benign prostatic hypertrophy did not appear to be related to systemic corticosteroid usage based on interaction models. The odds of diabetes mellitus type 2 was significantly increased in pemphigus vulgaris, even in the absence of systemic corticosteroid usage. In contrast, the odds of hypertension, osteoporosis, and insomnia were significantly increased in those who used systemic corticosteroids.

Cardiovascular disease risk factors, such as diabetes mellitus type 2 and hypertension [2, 5], and neuropsychiatric comorbidities, such as insomnia [8], have previously been demonstrated in pemphigus patients. In a nationwide inpatient sample, pemphigus was found to be associated with diabetes mellitus type 2, hypertension, osteoporosis, insomnia, cataracts, and numerous other comorbid health conditions [5]. In addition, a retrospective cohort study of 130 patients in Romania observed that

Table 4. Comorbidities of patients with mild or moderate-severe PV.

Comorbidity	Mild		Moderate/Severe	
	Adj OR (95% CI)	**P**	**Adj OR (95% CI)**	**P**
Type 2 diabetes mellitus	**3.48 (1.31-9.26)**	**0.01**	**7.15 (3.16-16.21)**	**<.0001**
Hypertension	1.24 (0.55-2.77)	0.6	**2.87 (1.44-5.73)**	**0.003**
Osteopenia	**11.08 (2.34-52.58)**	**0.003**	**8.55 (2.75-26.63)**	**0.0002**
Osteoporosis	1.73 (0.33-9.12)	0.5	**6.00 (1.81-19.93)**	**0.003**
Cataracts	**6.00 (1.10-32.76)**	**0.04**	4.00 (0.90-17.87)	0.07
Insomnia	-	-	**12.00 (1.34-107.37)**	**0.03**
BPH	4.37 (0.77-24.92)	0.1	**4.56 (1.05-18.95)**	**0.04**

BPH, benign prostatic hyperplasia.

Multivariate conditional logistic regression models with strata analysis to explore for associations between comorbidities and mild pemphigus vulgaris, moderate/severe pemphigus vulgaris, and pemphigus vulgaris without a history of steroid use. Only comorbidities that were significantly associated with pemphigus vulgaris in previous models were analyzed. Models controlled for age and sex.

Table 5. Comorbidities of pemphigus vulgaris patients with and without a history of systemic steroid usage.

Comorbidity	No PV, No steroids		PV, No steroids		PV, Steroids	
	Adj OR (95% CI)	P	Adj OR (95% CI)	P	Adj OR (95% CI)	P
Type 2 diabetes mellitus	1.0 [ref]	-	**3.71 (1.40-9.84)**	**0.01**	**5.85 (3.05-11.19)**	**<.0001**
Hypertension	1.0 [ref]	-	1.04 (0.37-2.94)	0.9	**2.81 (1.61-4.90)**	**0.0003**
Osteoporosis	1.0 [ref]	-	1.21 (0.16-8.97)	0.9	**7.33 (2.93-18.06)**	**<.0001**
Insomnia	1.0 [ref]	-	8.40 (0.72-97.05)	0.1	**10.95 (2.00-59.67)**	**0.006**

Multivariate logistic regression with interaction models were constructed to determine if history of systemic steroid usage was associated with an increased odds of having a certain comorbidity. Only comorbidities that were significantly associated with pemphigus vulgaris were analyzed in these models. Comorbidities that demonstrated at least a >20% increase in odds ratio between pemphigus patients with and without steroid usage were considered to demonstrate a statistically significant effect.

cardiovascular comorbidities, especially arrhythmia and coronary artery disease, were the strongest risk factors for mortality in pemphigus patients [9]. These cardiovascular risk factors – namely diabetes mellitus, hypertension, and obesity – should be addressed to prevent disease-related morbidity and mortality. Future guidelines for care of pemphigus patients should address best practices for screening and/or prevention of these and other comorbidities.

The present study suggests that decreased bone mineral density and cataracts occurring in pemphigus vulgaris is related to systemic corticosteroid usage, which is consistent with previous studies [5, 10]. Whereas, the associations of pemphigus vulgaris with benign prostatic hypertrophy and diabetes mellitus type 2 occurred in the absence of systemic corticosteroid usage. This raises intriguing questions about the contribution of systemic inflammation toward such associations. The mechanism of the association between pemphigus and benign prostatic hypertrophy is not known. However, chronic inflammation has been found to be associated with benign prostatic hypertrophy on prostate biopsy [11], with increased levels of pro-inflammatory cytokines [12]. Pemphigus is associated with systemic immune dysregulation of certain cytokines as well [13], suggesting that systemic inflammation may contribute to both pemphigus and benign prostatic hypertrophy. A previous cross-sectional study did not demonstrate an association between pemphigus and benign prostatic hypertrophy [1]. Regardless of the mechanisms, clinicians should be cognizant of the comorbid health conditions in pemphigus patients to minimize further morbidity and mortality. [1].

Despite the deleterious side-effects of systemic corticosteroids, they continue to be a mainstay of therapy in moderate-severe pemphigus. In the present cohort, 76% of pemphigus vulgaris patients had a history of taking systemic corticosteroids, with a mean duration of past use of 20.3 months. There is an increasing body of evidence for the efficacy of corticosteroid-sparing systemic agents, such as mycophenolate mofetil, azathioprine, and cyclophosphamide [14, 15]. The significantly increased rates of corticosteroid-associated comorbidities demonstrated in the present study support close monitoring for these corticosteroid-related side-effects and use non-steroidal systemic agents wherever possible.

This study has several strengths, including rigorous case definition of pemphigus based on histopathology, immunofluorescence and clinical findings. Another strength is that both outpatient and inpatient records were reviewed at a large quaternary care hospital and practice network in a major metropolitan city. However, there are several limitations. We identified 130 cases of any type of pemphigus and 102 cases of pemphigus vulgaris, in particular. While this is a large number of cases for these rare disorders, some analyses of rarer pemphigus subtypes and/or comorbid health disorders were underpowered. Moreover, disease severity was based on the physician's global assessment and did not use any standardized assessments, such as the pemphigus area and activity score. Medical documentation may

not have been complete in all cases. Finally, care of pemphigus patients may be funneled to certain dermatologists with interest in pemphigus, which may bias treatments and documentation. Future larger prospective studies are needed to confirm these associations and examine other less common comorbidities of pemphigus.

Conclusion

The present study demonstrated that pemphigus and its treatments are associated with a number of comorbid health conditions, including diabetes mellitus type 2, hypertension, decreased bone mineral density, cataracts, insomnia, and benign prostatic hypertrophy. The associations of pemphigus vulgaris with diabetes mellitus type 2 and benign prostatic hypertrophy were not related to systemic corticosteroid usage in interaction models. Increased surveillance for and strategies for prevention of relevant comorbidities are warranted in pemphigus patients. Finally, safer and more effective systemic treatment options are needed for pemphigus to minimize iatrogenic complications of disease.

References

1. Heelan K, Mahar AL, Walsh S, Shear NH. Pemphigus and associated comorbidities: a cross-sectional study. *Clin Exper Derm*. 2015;40(6):593-9. Epub 2015/03/20. [PMID: 25786337].
2. Ambiel MV, Roselino AM. Prevalence of Metabolic Syndrome and its components in a Brazilian sample of pemphigus patients. *An Bras Derm*. 2014;89(5):752-6. Epub 2014/09/04. [PMID: 25184914].
3. Parameswaran A, Attwood K, Sato R, Seiffert-Sinha K, Sinha AA. Identification of a new disease cluster of pemphigus vulgaris with autoimmune thyroid disease, rheumatoid arthritis and type I diabetes. *Br J Dermatol*. 2015;172(3):729-38. Epub 2014/10/02. [PMID: 25272088].
4. Schulze F, Neumann K, Recke A, Zillikens D, Linder R, Schmidt E. Malignancies in pemphigus and pemphigoid diseases. *J Invest Dermatol.* 2015;135(5):1445-7. Epub 2015/01/07. [PMID: 25560279].
5. Hsu DY, Brieva J, Sinha AA, Langan SM, Silverberg JI. Comorbidities and inpatient mortality for pemphigus in the U.S.A. *Br J Dermatol.* 2016;174(6):1290-8. Epub 2016/02/13. [PMID: 26864457].
6. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2014 2015 [May 3, 2015]. Available from: http://www.cdc.gov/diabetes/pdfs/data/2014-report-estimates-of-diabetes-and-its-burden-in-the-united-states.pdf.
7. Benjamini J, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J Roy Statist Soc Ser B* 1995;57(1):289-300
8. Ghodsi SZ, Chams-Davatchi C, Daneshpazhooh M, Valikhani M, Esmaili N. Quality of life and psychological status of patients with pemphigus vulgaris using Dermatology Life Quality Index and General Health Questionnaires. *J Dermatol.* 2012;39(2):141-4. Epub 2011/10/05. [PMID: 21967321].
9. Baican A, Chiorean R, Leucuta DC, Baican C, Danescu S, Ciuce D, Sitaru C. Prediction of survival for patients with pemphigus vulgaris and pemphigus foliaceus: a retrospective cohort study. *Orphanet J Rare Dis*. 2015;10(1):48. Epub 2015/04/22. [PMID: 25896794].
10. Wohl Y, Dreiher J, Cohen AD. Pemphigus and osteoporosis: a case-control study. *Arch Dermatol.* 2010;146(10):1126-31. Epub 2010/10/20. [PMID: 20956645].
11. Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, Kido M, Takahashi H, Kuk C, Kovylina M, Aldaoud N, Fleshner N, Finelli A, Klotz L, Lockwood G, Sykes J, Kwast T. Prevalence of inflammation and benign prostatic hyperplasia on autopsy in Asian and Caucasian men. *Euro Urol.* 2014;66(4):619-22. Epub 2014/07/12. [PMID: 25012523].
12. Kim HJ, Park JW, Cho YS, Cho CH, Kim JS, Shin HW, Chung DH, Kim SJ, Chun YS. Pathogenic role of HIF-1alpha in prostate hyperplasia in the presence of chronic inflammation. *Bioch Bophys Acta. 2013;*1832(1):183-94. Epub 2012/09/19. [PMID: 22986049].
13. 13. Lopez-Robles E, Avalos-Diaz E, Vega-Memije E, Hojyo-Tomoka T, Villalobos R, Fraire S, Domiguez-Soto L, Herrera-Esparza R. TNFalpha and IL-6 are mediators in the blistering process of pemphigus. *Int J Dermatol.* 2001;40(3):185-8. Epub 2001/06/26. [PMID: 11422521].
14. 14. Gurcan HM, Ahmed AR. Analysis of current data on the use of methotrexate in the treatment of pemphigus and pemphigoid. *Br J Dermatol.* 2009;161(4):723-31. Epub 2009/06/25. [PMID: 19548961].
15. 15. Esmaili N, Chams-Davatchi C, Valikhani M, Farshidfar F, Parvaneh N, Tamizifar B. Treatment of pemphigus vulgaris with mycophenolate mofetil as a steroid-sparing agent. *Eur J Dermatol:*. 2008;18(2):159-64. Epub 2008/04/22. [PMID: 18424375].