JAMA Dermatology | Original Investigation

Coexistent Solid Malignancies in Pemphigus
A Population-Based Study

Khalaf Kridin, MD; Shira Zelber-Sagi, PhD; Doron Comaneshter, PhD; Arnon D. Cohen, MD, PhD

IMPORTANCE The association of pemphigus vulgaris and pemphigus foliaceus with comorbid malignancies is yet to be firmly established.

OBJECTIVE To estimate the association between pemphigus and a wide range of nonhematologic malignancies using one of the largest cohorts of patients with pemphigus to date.

DESIGN, SETTING, AND PARTICIPANTS For this cross-sectional study, we used the computerized database of Clalit Health Services, the largest public health care provider organization in Israel insuring 4.4 million individuals in the settings of general community clinics, primary care and referral centers, and ambulatory and hospitalized health care. The study included 1985 patients with pemphigus and 9874 control patients and was conducted from January 2004 to December 2014.

MAIN OUTCOMES AND MEASURES The prevalence of 17 different solid malignancies was compared between patients diagnosed with pemphigus and age-, sex-, and ethnicity-matched control patients; χ^2 and *t* tests were used for univariate analysis, and a logistic regression model was used for multivariate analysis. The association was examined following a sensitivity analysis that included only cases treated with long-term pemphigus-specific medications (corticosteroids, immunosuppressants, or rituximab), and following the adjustment for several confounding factors.

RESULTS Overall, the total sample included 11 859 eligible patients, of whom 1985 were patients with pemphigus (mean [SD] age at presentation, 72.1 [18.5] years; 1188 women [59.8%]). In patients with pemphigus compared with control patients, there was a greater prevalence of esophageal cancers (0.4% vs 0.1%; odds ratio [OR], 2.9; 95% CI, 1.1-7.4) and laryngeal cancers (0.6% vs 0.3%; OR, 2.0; 95% CI, 1.0-4.1). No significant associations between pemphigus and other solid malignancies were observed. Estimates were not altered significantly after controlling for comorbidities, health care overutilization, immunosuppressive therapy, and other malignancy-specific risk factors (ie, smoking and alcohol abuse in laryngeal cancer, gastroesophageal reflux disease in esophageal cancer).

CONCLUSIONS AND RELEVANCE Significant associations were observed between pemphigus and solid malignancies of the larynx and the esophagus. Physicians treating patients with pemphigus should be aware of these findings. Further observational studies are warranted to establish this association in other cohorts.

JAMA Dermatol. 2018;154(4):435-440. doi:10.1001/jamadermatol.2017.6334
Published online February 16, 2018.

Author Affiliations: Department of Dermatology, Rambam Health Care Campus, Haifa, Israel (Kridin); School of Public Health, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel (Zelber-Sagi); Department of Quality Measurements and Research, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel (Comaneshter, Cohen); Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel (Cohen).

Corresponding Author: Khalaf Kridin, MD, Department of Dermatology, Rambam Health Care Campus, PO Box 9602, Haifa 31096, Israel (dr_kridin@hotmail.com).

Pemphigus is a rare intraepithelial autoimmune blistering disease characterized by painful vesiculobullous lesions on the skin and mucous membranes. It is mediated by immunoglobulin G autoantibodies against both desmoglein-3 and/or desmoglein-1, transmembrane glycoprotein cadherins responsible for intercellular adhesion of epidermal keratinocyte. These antibodies bind to keratinocyte desmosomes causing loss of cell-to-cell adhesion and blister formation through a process termed acantholysis, whether by a direct effect on desmosomal adherens or by triggering a cellular process that results in acantholysis.[1,2] The prognosis for patients with pemphigus has greatly improved since the introduction of corticosteroid therapy; nevertheless, pemphigus remains a potentially life-threatening disease, with the risk of death among pemphigus patients being 2-to-3-fold higher than for the general population.[3-5]

The association of pemphigus vulgaris and foliaceus with comorbid nonhematological malignancies is yet to be established. In a recent German case-control study,[6] pemphigus vulgaris was found to be associated with oropharyngeal (odds ratio [OR], 7.2; 95% CI, 2.7-19.9), gastrointestinal (OR, 2.6; 95% CI, 1.9-3.5), and colon (OR, 2.4; 95% CI, 1.6-3.6) cancers, whereas pemphigus foliaceus was associated with nonmelanoma skin cancer (OR, 2.5; 95% CI, 1.4-4.0). Ogawa et al[7] reported that the prevalence of internal malignancies among 496 Japanese patients with pemphigus (5.0%) was higher than expected in the general Japanese population (0.6%). Lung cancer was the most frequent solid malignancy in this study. It is noteworthy that no age- and sex-matched control group was enrolled in this study.

Apart from these studies, the association of pemphigus with solid tumors was not assessed systematically. The aim of the current study was to estimate the association between pemphigus and a broad range of solid tumors using one of the largest cohorts of patients with pemphigus to date.

Key Points

Question Is there an association between pemphigus and solid malignancies?

Findings This large-scale population-based study of 1985 patients with pemphigus revealed a statistically significant comorbidity between pemphigus and 2 solid malignancies: esophageal and laryngeal cancers. This association retained its statistical significance following a multivariate and sensitivity analyses; solid malignancies in other sites were not increased among patients with pemphigus.

Meaning Clinicians should be aware of this association and further research is warranted to establish this association in other cohorts.

Methods

Study Design and Data Set

This study was designed as a cross-sectional retrospective study using the computerized database of Clalit Healthcare Services (CHS)—the largest managed-care organization in Israel, serving a population of approximately 4 500 000 enrollers in 2016. Clalit Healthcare Services has a comprehensive database with continuous real-time input from medical, pharmaceutical, and administrative computerized operating systems. The validity of diagnoses in this registry, which are grounded on hospital and primary care physicians and specialists reports, has been shown to be reliable.[8,9] This database undergoes a consistent validation process by logistic checks (such as comparing the diagnoses from various sources), as well as by direct validation of the diagnoses by the treating physicians. This study was approved by the institutional ethics board of Ben-Gurion University and CHS. Informed consent was not warranted because the data are anonymized and because this is a noninterventional observational study that does not require informed consent according to Israeli law.

Study Population and Covariate Factors

Cases were defined as having pemphigus when there was a documented diagnosis of pemphigus at least twice in the medical records registered by a physician in the community or when pemphigus had been registered in the diagnoses of discharge letters from hospitals. Up to 5 control patients, who never were diagnosed with pemphigus, were randomly selected for each patient in the pemphigus cohort. The control group was randomly selected from the list of CHS members matched to cases regarding sex, age, and ethnicity, and thus sampling the general population. Age matching was based on the exact year of birth (1-year strata). Controls were ensured to be alive and contributing data to CHS on the date of the diagnosis of the matched case. A date of "pseudodiagnosis" was assigned to each control patient, which was the date of diagnosis of the matched case.

Data available from the CHS database included age, sex, socioeconomic status (SES), and diagnoses of chronic diseases. These diagnoses were extracted from the CHS registry on chronic diseases, which is based on data from hospital and primary care physicians' reports and validated by primary physicians.

Outcome measures were adjusted for comorbidities as determined using Charlson comorbidity index, excluding the malignant component of this index, specifically metastatic solid tumor, leukemia (acute or chronic), lymphoma, and tumors without metastases.[10] The Charlson index is a weighted index reflecting the degree of comorbidity of a patient by taking into account the number and severity of comorbid conditions. It is a validated method of measuring comorbidity that has been illustrated to be a sensitive predictor of prognosis.[10] Charlson scores, based on the presence or absence of 19 medical conditions, give a continuous score which is then categorized into comorbidity scores of "none" (0), "moderate" (1-2), and "severe" (>2). Outcome measures were also adjusted for overutilization of health services, to ensure that observed associations were not merely due to increased ascertainment. Health care utilization was determined by the number of total visits per individual in the year before the diagnosis of pemphigus in cases and "pseudodiagnosis" in controls. The outcome measures were further adjusted for immunosuppressive treatment, which was defined as the prescription of at least one of the following

agents for more than 6 months: azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate.

Statistical Analysis

The distribution of sociodemographic and clinical factors was compared between patients with and without pemphigus using the χ^2 test for sex and socioeconomic status, and the *t* test for age. Logistic regression was then used to calculate ORs and 95% CIs to compare cases and controls with respect to the specified malignancies. Homogeneity of ORs across strata was tested using Breslow-Day and Tarone tests. The exact age matching permitted the use of unconditional logistic regression.[11] All statistical analysis was performed using SPSS software, version 23 (IBM Analytics).

Results

The total sample included 11 859 eligible patients, of whom 1985 were patients with pemphigus, and 9874 patients were age-, sex-, and ethnicity-matched controls. The mean (SD) age at presentation of pemphigus was 72.1 (18.5) years, which is identical to the age of control patients at the date of their enrollment. In all, 1188 cases (59.8%) were women, and a similar proportion was seen in controls. The ethnic and the socioeconomic structure of the 2 groups was comparable. Comorbidity rates, measured by the Charlson index, were higher in cases, with 1059 patients (53.4%) having severe comorbidity compared with 4055 patients (41.1%) in the control group ($P < .001$). Lower rate of smoking was registered in the pemphigus group (25.7% vs 27.9%; $P = .045$) (**Table 1**).

In the pemphigus group compared with the control group, there was a significantly higher prevalence of esophageal cancer (0.4% vs 0.1%; $P = .02$) and laryngeal cancer (0.6% vs 0.3%; $P = .04$). The prevalence of the following malignancies did not differ significantly between patients with pemphigus and their matched control patients: cancers of pharynx, thyroid, colon and rectum, pancreas, urinary bladder, brain and central nervous system (CNS), bone, lung, prostate, stomach, liver and bile ducts, kidney, cervix, and ovary (**Table 2**).

Table 2 presents the results of univariate and logistic regression models and summarizes ORs for nonhematological malignancies in patients with pemphigus across the entire study sample. There was a 3-fold increase in the odds of esophageal cancer (OR, 2.9; 95% CI, 1.1-7.4) and a 2-fold increase in the odds of laryngeal cancer (OR, 2.0; 95% CI 1.0-4.1) among patients with pemphigus relative to control patients.

Adjusting for comorbidity did not remove the 2 significant associations (Table 2). Interestingly, health care utilization rates were higher in controls than in cases, with 71% of controls and 65% of cases having more than 12 consultations in the year before pemphigus diagnosis (Table 1). Adjustment for utilization of health services led to the association between pemphigus and laryngeal cancer being of borderline statistical significance (adjusted OR, 1.9; 95% CI, 0.96-3.91), as well as to the emergence of pemphigus as a protective factor for prostate cancer (adjusted OR, 0.7; 95% CI, 0.52-1.00) (Table 2).

To confirm the association of pemphigus with esophageal and laryngeal cancers, we further performed a multivariate logistic regression model to control for putative confounding factors. After controlling for demographic variables, smoking, alcohol abuse, gastroesophageal reflux disease (GERD), peptic ulcer disease, health care utilization, and comorbidities, pemphigus demonstrated a stronger independent association with esophageal cancer (multivariate OR, 3.8; 95% CI, 1.16-12.31). GERD and alcohol abuse were also independently associated with esophageal cancer (**Table 3**). Adjusting for demographic variables, smoking, alcohol abuse, GERD, health care utilization, and comorbidities revealed an independent association between pemphigus and laryngeal cancer (multivariate OR, 2.1; 95% CI, 1.03-4.30). Older age, smoking, and alcohol abuse were also independently associated with esophageal cancer (**Table 4**).

Table 1. Descriptive Characteristics of the Study Participants

Characteristic	Patients With Pemphigus (n = 1985)	Controls (n = 9874)	*P* Value
Age, y			
Mean (SD)	72.1 (18.5)	72.1 (18.5)	>.99
Median (range)	77.4 (0-103.0)	77.4 (0-103.1)	
Male sex, No. (%)	797 (40.2)	3962 (40.1)	.93
Ethnicity, No. (%)			
Jewish	1805 (90.9)	8866 (89.8)	.14
Arabs	180 (9.1)	1008 (10.2)	
BMI, mean (SD)	27.7 (6.6)	27.9 (6.6)	.36
Smoking, No. (%)	510 (25.7)	2758 (27.9)	.045
Alcohol abuse, No. (%)	23 (1.2)	84 (0.9)	.19
GERD, No. (%)	326 (16.4)	1496 (15.2)	.15
Charlson comorbidity score, No. (%)			
None (0)	344 (17.3)	2636 (26.7)	<.001
Moderate (1-2)	582 (29.3)	3183 (32.2)	.01
Severe (≥3)	1059 (53.4)	4055 (41.1)	<.001
Health care utilization, No. (%)			
0 Visits	286 (14.4)	770 (7.8)	<.001
1-12 Visits	411 (20.7)	2094 (21.2)	.25
≥13 Visits	1288 (64.9)	7010 (71.0)	<.001
SES, No. (%)			
Low	634 (31.9)	3249 (32.9)	.39
Intermediate	830 (41.8)	4263 (43.2)	.25
High	423 (21.3)	2217 (22.5)	.24

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GERD, gastroesophageal reflux disease; SES, socioeconomic status.

Discussion

Our population-based large-scale study revealed an approximately 3-fold and 2-fold higher prevalence of esophageal and laryngeal cancers, respectively, among patients with pemphigus compared with the general population of similar age, sex, and ethnicity. Conversely, no significant association was observed between pemphigus and other nonhematological malignancies.

Table 2. The Association Between Pemphigus and Nonhematologic Malignancies

Cancer	No. (%)		OR (95% CI)	Univariate *P* Value	Adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]
	Pemphigus (n = 1985)	Controls (n = 9874)				
Esophagus	7 (0.4)	12 (0.1)	2.91 (1.14-7.40)	.02	2.72 (1.06-6.98)	2.82 (1.10-7.23)
Larynx	11 (0.6)	27 (0.3)	2.03 (1.01-4.10)	.04	1.96 (0.99-3.98)	1.92 (0.96-3.91)
Pharynx	9 (0.5)	40 (0.4)	1.12 (0.54-2.31)	.76	1.03 (0.49-2.14)	1.07 (0.52-2.22)
Thyroid	13 (0.7)	47 (0.5)	1.38 (0.74-2.55)	.31	1.41 (0.76-2.63)	1.23 (0.66-2.29)
Colorectal	75 (3.8)	399 (4.0)	0.93 (0.73-1.20)	.59	0.83 (0.64-1.07)	0.88 (0.68-1.13)
Pancreas	7 (0.4)	35 (0.4)	1.00 (0.44-2.24)	.99	0.94 (0.42-2.14)	0.98 (0.43-2.22)
Urinary bladder	24 (1.2)	157 (1.6)	0.76 (0.49-1.17)	.21	0.64 (0.42-0.99)	0.70 (0.45-1.08)
Brain and CNS	6 (0.3)	28 (0.3)	1.01 (0.44-2.58)	.89	1.11 (0.46-2.71)	1.02 (0.42-2.48)
Bone	2 (0.1)	13 (0.1)	0.77 (0.17-3.39)	.72	0.63 (0.14-2.83)	0.61 (0.14-2.75)
Lung	17 (0.9)	119 (1.2)	0.71 (0.43-3.39)	.14	0.64 (0.38-1.07)	0.67 (0.40-1.12)
Prostate	43 (2.2)	268 (2.7)	0.79 (0.57-1.10)	.16	0.69 (0.50-0.97)	0.72 (0.52-1.00)
Uterus	7 (0.4)	47 (0.5)	0.74 (0.33-1.64)	.46	0.75 (0.34-1.68)	0.68 (0.30-1.51)
Stomach	12 (0.6)	68 (0.7)	0.88 (0.47-1.62)	.68	0.83 (0.45-1.55)	0.83 (0.45-1.55)
Liver and bile ducts	3 (0.2)	27 (0.3)	0.55 (0.17-1.82)	.32	0.44 (0.13-1.47)	0.52 (0.16-1.73)
Kidney	13 (0.7)	77 (0.6)	0.84 (0.47-1.51)	.56	0.71 (0.39-1.30)	0.76 (0.42-1.37)
Cervix	1 (0.1)	16 (0.2)	0.31 (0.04-2.34)	.23	0.35 (0.05-2.64)	0.29 (0.04-2.22)
Ovary	8 (0.4)	27 (0.3)	1.48 (0.67-3.25)	.33	1.41 (0.64-3.13)	1.42 (0.64-3.14)

Abbreviations: CNS, central nervous system; OR, odds ratio.

[a] Adjusted for Charlson score not including malignant diseases.

[b] Adjusted for health care utilization.

Our findings are coherent with a recent case-control study[6] that suggested that pemphigus vulgaris was found to be associated with gastrointestinal cancers. The diagnosis code of the latter includes, among other, all malignant tumors of the esophagus. Nevertheless, the reported association of pemphigus with colon and oropharyngeal cancers was not reproduced in our study. Of note, the findings of the study above were extracted solely from a univariate analysis without adjusting for putative confounding factors which may influence the outcomes reported.[6] The effect of various genetic and geographic factors may also contribute to the differences between the studies. However, the 2.3-fold larger sample size, the adjustments for multiple confounders, and the existence of biological plausibility[12] argue in favor of our findings.

The interpretation of the existence of pemphigus and laryngeal or esophageal cancer in a single individual has not been fully elucidated. However, it is apparent that both the laryngeal and esophageal mucosae can be involved in the course of pemphigus vulgaris,[13-16] as both express desmoglein 3, the main autoantigen implicated in the pathogenesis of the disease.[17] The putative mechanism underlying this relationship relies heavily on the temporal sequence of the diagnoses (whether the malignancy preceded or followed pemphigus). It can be alleged that malignant tumors may induce tissue damage and morphological alterations in the epithelial surface antigens of the laryngeal and esophageal mucosae. Hence, certain antigens that were previously concealed from the immune system become exposed, thus inducing a secondary autoimmune response, a concept known as "epitope spreading phenomenon."[18] On the other hand, chronic and persistent inflammation in these tissues, as a result of the activity of pemphigus, may eventually contribute to the development of carcinogenesis and neoplasia[19] via inducing proneoplastic mutations, resistance to apoptosis, and environmental changes such as stimulation of angiogenesis.[19-21] Much of the understanding of the association between chronic inflammation and cancer was illustrated through the association between chronic inflammatory bowel diseases and the increased risk of colon carcinoma.[22] The hypothesis that immunosuppressive agents may have triggered malignancy[23] was refuted by the multivariate analysis indicating that pemphigus was associated with these malignancies independently of treatment with immunosuppressive therapy. Further studies shedding light on the cumulative incidence of these malignancies among pemphigus patients are highly warranted to better understand the mechanism of the coexistence of pemphigus with these cancers.

The significant association of increasing age with laryngeal cancer in our study population accords with the increasing trend for internal malignancies with aging among Japanese patients with pemphigus.[7] A similar pattern was not detected among patients with bullous pemphigoid in the same study.[7]

Strengths

Our study is a large, population-based study of an uncommon condition that enables reasonably precise estimation of prevalence rates which have otherwise been unavailable. Thus, it is less susceptible to selection bias than other study designs. The large size of the data set gives sufficient power to exclude chance as the basis for the positive associations observed. We used one of the largest cohorts of patient with pemphigus reported so far, overcoming one of the main hindrances in the research of pemphigus, as the lack of large-scale clinical data are a major

Table 3. A Multivariate Logistic Regression Analysis of Predictors for Esophageal Cancer

Variable	OR (95% CI)	*P* Value
Pemphigus	3.79 (1.16-12.31)	.03
Age (per year)	1.00 (0.96-1.05)	.97
Male sex	0.72 (0.18-2.84)	.64
Jewish ethnicity vs Arabs	0.44 (0.09-2.25)	.33
BMI	1.00 (0.92-1.10)	.96
GERD	5.82 (1.70-19.87)	.01
Peptic ulcer disease	1.79 (0.47-6.85)	.39
Smoking	0.68 (0.16-2.91	.60
Alcohol abuse	11.69 (1.20-113.63)	.03
Immunosuppressive therapy	NA	.99
Health care utilization	0.99 (0.97-1.01)	.53
Charlson comorbidity score, without malignancy	0.99 (0.73-1.36)	.97

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GERD, gastroesophageal reflux disease; NA, not applicable; OR, odds ratio.

Table 4. A Multivariate Logistic Regression Analysis of Predictors for Laryngeal Cancer

Variable	OR (95% CI)	*P* Value
Pemphigus	2.10 (1.03-4.30)	.04
Age, per year	1.03 (1.01-1.06)	.01
Male sex	1.97 (0.98-3.96)	.06
Jewish ethnicity vs Arabs	1.63 (0.38-6.88)	.51
GERD	0.71 (0.27-1.85)	.49
Smoking	2.32 (1.16-4.64)	.02
Alcohol abuse	11.69 (1.20-113.63)	.03
Immunosuppressive therapy	0.415 (0.05-3.18)	.40
Health care utilization	1.01 (0.99-1.02)	.16
Charlson comorbidity score, without malignancy	0.91 (0.76-1.09)	.30

Abbreviations: GERD, gastroesophageal reflux disease; OR, odds ratio.

impediment to a better understanding of pemphigus associations and comorbidities. The existence of ascertainment bias was ruled out when our outcome measures reproduced following the adjustment for overutilization of health care system. The probability of misdiagnosis of paraneoplastic pemphigus is highly unlikely because the diagnosis of pemphigus is clearly differentiated from the latter by *International Classification of Diseases, Ninth Revision*, codes. Moreover, paraneoplastic pemphigus is a highly rare condition occurring mainly in conjunction with non-Hodgkin lymphoma and chronic lymphocytic leukemia, and less frequently with nonhematological solid tumors.[24,25]

Limitations

The study limitations include the lack of data concerning the immunopathological subtype, clinical characteristics, and severity of pemphigus, as well as the precise histological type of each cancer. Owing to the cross-sectional design of the study, limited conclusions should be drawn regarding a causal association between the entities.[12] The use of routinely collected data did not enable us to validate the diagnoses directly; however, we believe it is unlikely that important misclassification will have meaningfully affected our findings. The diagnoses of both pemphigus and malignancies in our study is of reliable validity, because pemphigus in Israel is diagnosed in secondary and tertiary care facilities, relying on skin biopsies, direct and indirect immunofluorescence,[26] and because the chronic diseases registry of CHS is cross-linked with the Israel National Cancer Registry.

Conclusions

Significant associations were observed between pemphigus and solid malignancies of the larynx and the esophagus. Physicians treating patients with pemphigus should be aware of this association. Further prospective studies are necessary to confirm these associations in other cohorts as well.

ARTICLE INFORMATION

Accepted for Publication: December 16, 2017.

Published Online: February 16, 2018. doi:10.1001/jamadermatol.2017.6334

Author Contributions: Drs Kridin and Cohen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kridin, Zelber-Sagi, Cohen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kridin, Zelber-Sagi.
Critical revision of the manuscript for important intellectual content: Kridin, Comaneshter, Cohen.
Statistical analysis: Kridin, Comaneshter, Cohen.
Obtained funding: Zelber-Sagi.
Administrative, technical, or material support: Kridin, Cohen.
Study supervision: Kridin, Zelber-Sagi, Cohen.

Conflict of Interest Disclosures: None reported.

Meeting Presentation: This study was presented at the 2018 American Academy of Dermatology Annual Meeting; February 16, 2018; San Diego, California.

REFERENCES

1. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med*. 2006;355(17):1800-1810.

2. Sitaru C, Zillikens D. Mechanisms of blister induction by autoantibodies. *Exp Dermatol*. 2005;14(12):861-875.

3. Kridin K, Sagi SZ, Bergman R. Mortality and cause of death in patients with pemphigus. *Acta Derm Venereol*. 2017;97(5):607-611.

4. Huang Y-H, Kuo C-F, Chen Y-H, Yang Y-W. Incidence, mortality, and causes of death of patients with pemphigus in Taiwan: a nationwide population-based study. *J Invest Dermatol*. 2012;132(1):92-97.

5. Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJP, West J. Bullous pemphigoid and pemphigus vulgaris–incidence and mortality in the UK: population based cohort study. *BMJ*. 2008;337:a180.

6. Schulze F, Neumann K, Recke A, Zillikens D, Linder R, Schmidt E. Malignancies in pemphigus and pemphigoid diseases. *J Invest Dermatol*. 2015;135(5):1445-1447.

7. Ogawa H, Sakuma M, Morioka S, et al. The incidence of internal malignancies in pemphigus and bullous pemphigoid in Japan. *J Dermatol Sci*. 1995;9(2):136-141.

8. Rennert G, Peterburg Y. Prevalence of selected chronic diseases in Israel. *Isr Med Assoc J*. 2001;3(6):404-408. Accessed January 30, 2017.

9. Birkenfeld S, Dreiher J, Weitzman D, Cohen AD. Coeliac disease associated with psoriasis. *Br J Dermatol*. 2009;161(6):1331-1334.

10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic

comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

11. Pearce N. Analysis of matched case-control studies. *BMJ*. 2016;352:i969.

12. Höfler M. The Bradford Hill considerations on causality: a counterfactual perspective. *Emerg Themes Epidemiol*. 2005;2:11.

13. Gomi H, Akiyama M, Yakabi K, Nakamura T, Matsuo I. Oesophageal involvement in pemphigus vulgaris. *Lancet*. 1999;354(9192):1794.

14. Chang S, Park SJ, Kim SW, et al. Esophageal involvement of pemphigus vulgaris associated with upper gastrointestinal bleeding. *Clin Endosc*. 2014;47(5):452-454.

15. Mignogna MD, Lo Muzio L, Galloro G, Satriano RA, Ruocco V, Bucci E. Oral pemphigus: clinical significance of esophageal involvement: report of eight cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;84(2):179-184.

16. Robati RM, Rahmati-Roodsari M, Dabir-Moghaddam P, et al. Mucosal manifestations of pemphigus vulgaris in ear, nose, and throat; before and after treatment. *J Am Acad Dermatol*. 2012;67(6):e249-e252.

17. The Human Protein Atlas. Tissue expression of DSG3—Summary. http://www.proteinatlas.org/ENSG00000134757-DSG3/tissue. Accessed January 7, 2017.

18. Chan LS, Vanderlugt CJ, Hashimoto T, et al. Epitope spreading: lessons from autoimmune skin diseases. *J Invest Dermatol*. 1998;110(2):103-109.

19. Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncology (Williston Park)*. 2002;16(2):217-226.

20. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860-867.

21. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883-899.

22. Ekbom A, Helmick C, Zack M, Adami H-O. Ulcerative colitis and colorectal cancer: a population-based study. *N Engl J Med*. 1990;323(18):1228-1233.

23. Mabrouk D, Gürcan HM, Keskin DB, Christen WG, Ahmed AR. Association between cancer and immunosuppressive therapy–analysis of selected studies in pemphigus and pemphigoid. *Ann Pharmacother*. 2010;44(11):1770-1776.

24. Ohzono A, Sogame R, Li X, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. *Br J Dermatol*. 2015;173(6):1447-1452.

25. Nguyen VT, Ndoye A, Bassler KD, et al. Classification, clinical manifestations, and immunopathological mechanisms of the epithelial variant of paraneoplastic autoimmune multiorgan syndrome: a reappraisal of paraneoplastic pemphigus. *Arch Dermatol*. 2001;137(2):193-206.

26. Kridin K, Zelber-Sagi S, Khamaisi M, Cohen AD, Bergman R. Remarkable differences in the epidemiology of pemphigus among two ethnic populations in the same geographic region. *J Am Acad Dermatol*. 2016;75(5):925-930.

NOTABLE NOTES

Hulusi Behçet—A Life of Passion and Endeavor in Dermatology

Aria Shakeri, HBSc

Hulusi Behçet, the famous Turkish dermatologist, was born on February 20, 1889, in Istanbul.[1] He endured a difficult and gloomy childhood during which he lost his mother and also experienced insomnia, colitis, and angina pectoris, resulting in him growing up to be an introverted man.[1] He undertook his primary education in Damascus; he was taken there because of his father's business affairs. In 1906 and at the age of 16, he started his medical studies in the Kuleli Military Medical School, graduating in 1910.[2] Dr Behçet then undertook specialist training in dermatology and venereal diseases at Gülhane Military Hospital until 1914.[3] During the First World War (1914-1918), he served as a dermatovenereologist in the Edirne Military Hospital. After the war, he traveled to Europe to further his training and had stays in Berlin and Budapest. However, he soon returned to Turkey and in 1923 was appointed the head physician of Hasköy Venereal Diseases Hospital.[2] Later, he established the department of dermatology and venereology in the University of Istanbul and served as its head until 1947.[3]

Dr Behçet was a prolific academician who published more than 100 articles in various national and international meetings and was also known for his frequent travels to forge academic collaborations.

Today, he is widely known in the medical community because of the disease that bears his name. It was his longstanding relationship with 3 patients with complicated illnesses that led to Behçet's brilliant idea of a single clinical entity being responsible for the seemingly unrelated findings. He connected the major observations of aphthous ulcers of mouth and genitalia to the ophthalmologic inflammatory findings and synthesized them as a new disorder.[1] In 1936, he first reported these ideas in a meeting and a year later published them in the journal *Dermatologische Wochenschrift*.[3] Soon, clinicians from across the world reported findings and observations consistent with Behçet's ideas. In 1947 during the International Geneva Medical Congress, Professor Mirschner (from the Zurich Faculty of Medicine) requested that the disease entity be named "Morbus Behçet."[1] Today, Behçet disease is recognized as a vasculitic disorder with protean manifestations that can even affect the joints, brain, and the gastrointestinal system.

In addition, Behçet produced pioneering work in the fields of parasitosis, fig dermatitis, and leishmaniasis and also started the first dermatovenereology journal of Turkey.[1] One of his most important contributions to Turkish dermatology was the publication (in 1940) of the monograph "Clinical and Practical Syphilis, Diagnosis and Related Dermatoses," in which he meticulously described various aspects of syphilis.[2]

Behçet died from a sudden myocardial infarction on March 8, 1948. The scientific community remembers him for his intellectual curiosity, academic proficiency, and clinical brilliance.

Author Affiliation: University of Virginia School of Medicine, Charlottesville.

Corresponding Author: Aria Shakeri, HBSc, University of Virginia School of Medicine, 1215 Lee St, Charlottesville, VA 22908 (as4qb@hscmail.mcc.virginia.edu).

1. Tüzün Y. Hulusi Behçet, MD: February 20, 1889 to March 8, 1948. *Clin Dermatol*. 2006;24(6):548-550.

2. Tan SY, Poole PS. Hulusi Behçet (1889-1948): passion for dermatology. *Singapore Med J*. 2016;57(7):408-409.

3. Saylan T. Life story of Dr. Hulusi Behçet. *Yonsei Med J*. 1997;38(6):327-332.