CLINICAL REPORT

Development of a Disease Registry for Autoimmune Bullous Diseases: Initial Analysis of the Pemphigus Vulgaris Subset

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Pemphigus vulgaris (PV) is a rare, potentially life threatening, autoimmune blistering skin disease. The International Pemphigus and Pemphigoid Foundation (IPPF) has recently developed a disease registry with the aim to enhance our understanding of autoimmune bullous diseases with the long-term goal of acquiring information to improve patient care. Patients were recruited to the IPPF disease registry through direct mail, e-mail, advertisements, and articles in the IPPF-quarterly, -website, -Facebook webpage, and IPPF Peer Health Coaches to complete a 38-question survey. We present here the initial analysis of detailed clinical information collected on 393 PV patients. We report previously unrecognized gender differences in terms of lesion location, autoimmune comorbidity, and delay in diagnosis. The IPPF disease registry serves as a useful resource and guide for future clinical investigation. *Key words: autoimmune bullous disease; disease registry; epidemiology; pemphigus vulgaris.*

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Pemphigus vulgaris (PV) is an autoimmune skin disease in which autoantibodies primarily bind to the cadherin-family adhesion molecule desmoglein (DSG) 3, and in some cases DSG 1. Antibody attachment causes interference in cell-to-cell adherence that ultimately leads to keratinocyte acantholysis, resulting in an intraepithelial blister (1, 2). Any epidermal area, both mucosal and cutaneous, can be affected.

While PV is rare (world-wide incidence is reported to be from 0.5–3.2 per 100,000 people) (3–5), it can have devastating effects on those afflicted. Lesions can be extremely painful and lead to secondary infections. The etiology is unknown and many triggering factors have been suggested including medications, diet, and environmental exposures (6–9). Most often there is a need for long-term immunosuppressive therapy which can add to the disease burden due to the potential side effects of these drugs.

Presently, the lack of large-scale clinical data is a major impediment to a better understanding of disease processes and management strategies in PV. The rare nature of PV makes the collection of epidemiologic data of a substantial number of patients difficult and time consuming. To date, there have been few epidemiologic studies in PV, all conducted with limited data sets (3–5, 10–12), including an anonymous internet-based survey of 171 PV patients by our group (13).

The creation of a comprehensive and readily accessible database to facilitate data collection is a necessary step to expedite future large-scale analyses focused on a variety of different data parameters. For this purpose, the International Pemphigus and Pemphigoid Foundation (IPPF), in conjunction with members of its medical advisory board, established a disease registry for the systematic and comprehensive collection of clinical information using a standardized template. The aim of this effort was to amalgamate information on autoimmune blistering patients worldwide, track patients over time, and facilitate the future collection of tissue and blood samples linked to defined clinical information.

This report represents the first analysis of the IPPF registry data after enrollment of 599 patients, including 393 PV patients, over a 19-month period. Our data confirm results from previous epidemiologic studies in PV and reveals previously unknown differences between males and females in terms of lesion location, autoimmune comorbidity, and delay in diagnosis.

MATERIAL AND METHODS

Registry development, patient recruitment, and data acquisition

The IPPF Patient Disease Registry utilizes a series of questions using branch logic to guide participants through only the areas they qualify to answer and help respondents stay focused, thereby increasing completion rates and decreasing erroneous responses. Questions were asked in a variety of formats including text-based, drop down selection, and radio selection. Questions using forced-choice responses were developed to ensure standardized answers based on probable responses to the question being asked.

The survey consisted of questions regarding general demographic information followed by 38 questions on disease activity/characteristics, medical care, and medical therapy. Submissions were allowed only after the respondent had completed all questions derived from the logic path individually developed by the survey engine based on answers to previous questions. Not all respondents answered the same set of treatment and history questions based on their current disease activity, past medications, and current treatments. The questions were created by IPPF board members, including Drs. D. Sirois, B. Rengarajan, and P. Konowitz, in collaboration with IPPF medical advisory board members Drs. A. A. Sinha and V. P. Werth, and IPPF Senior Peer Health Coach M. Yale. The study was approved by the Western Institutional Review Board (#20100317).

Patients were recruited through direct mail, e-mail, advertisements, articles in the IPPF- quarterly, -website, -Facebook webpage, and by invitation during 1:1 conversation with Peer Health Coaches (recruitment was done internationally, however direct mail was only sent within the USA). Participating patients filled out a questionnaire accessible through the IPPF website at http://www.pemphigus.org/research/registry/ (powered by survey gizmo version 16), or were mailed a form (English and Spanish versions were available) if they did not have internet access. The data collected and analyzed in this report is from patients enrolled between 4/14/2010–11/20/2011. The survey was compliant with HIPAA and took approximately 15 min to complete. Of the 424 registry entries that identified their disease as PV, 393 completed the survey (92.69% retention rate). Patients who had additional questions, wanted more information, or wanted to donate tissue/blood samples to aid in research had the option to be contacted. Two hundred and sixty-nine participants (190 females; 79 males) indicated their willingness to donate blood and 223 participants wanted to donate tissue (156 females; 67 males).

Statistical analysis and data interpretation

Data was exported from survey gizmo (or written input in the case of paper surveys) to Excel format. An exact Pearson Chi-square test was used to assess the association between categorical variables. The lambda coefficient (Λ) was used to measure the degree of the relationship when nominal data were present. Kendall's tau (τ) was used to measure the strength and direction of the relationship between ordinal variables. Microsoft Excel 2007 and SAS v9.3 (Cary, NC) were used for data analysis at a significance level of 0.05.

When comparing data across questions, inconsistencies arose in a low percentage of study participants ($<1\%$). For example, a survey participant might report no current lesions in one question and yet in another question indicate the presence of current lesions. Uninterpretable data from patients were either removed from the overall analysis or interpreted based on answers to other corresponding questions; therefore, the number of patients included in the analysis of different parameters may differ slightly between analyses. Since patients did not report their weight, mean weights according to the CDC (14) were used for males (88.7 kg) and females (75.4 kg) in order to determine the level of therapy (minimal vs. more than minimal) as defined by Murrell et al. (15).

RESULTS

Study population and demography

A total of 599 patients with pemphigus or pemphigoid disease answered the IPPF questionnaire over a 19-month period. The majority of participants reported a diagnosis of PV ($n=393$), followed by bullous pemphigoid ($n=64$), pemphigus foliaceous ($n=58$), ocular cicatricial pemphigoid/mucous membrane pemphigoid ($n=50$), cicatricial pemphigoid ($n=31$), and paraneoplastic pemphigus ($n=3$). The female:male ratio among PV patients was 2.54:1, with a mean age at diagnosis of 45.7 years (range 5–82 years; standard deviation 14.0 years) and a Caucasian majority (73.5%) (Table SI[1]). Of the 393 PV patients, 303 were living and diagnosed in the USA at the time of disease onset, with the majority residing in the Northeast followed by the Pacific-Coastal region (Fig. S1[1]). The remainder resided in other countries at the start of illness: 31 in Europe, 24 in Asia, 12 in non-USA North America, 12 in Australia, 7 in South America, and 3 in Africa (1 subject was omitted due to conflicting data).

Disease characteristics

The survey included 10 questions regarding disease characteristics. These focused on lesion location, number of lesions, history of lesion location, global illness activity, and comorbid autoimmune diseases. Of the 393 PV patients, 215 (54.7%) had lesions at the time of study participation; 45.8% had mucosal only, 29.6% had mucocutaneous, and 24.5% had cutaneous only manifestations. When separated by gender we found a statistically significant difference between lesion location and gender (male: 39% cutaneous only, 23% mucosal only, and 38% mucocutaneous; female: 19% cutaneous only, 55% mucosal only, and 26% mucocutaneous), with females more likely to have mucosal only lesions and males more likely to have cutaneous only or mucocutaneous lesions ($p<0.001$, $\Lambda=0.055$) (Fig. S2[1]).

Patients were asked to determine their "global illness activity" (defined as (*i*) no lesions and taking medication, (*ii*) no lesions and not taking medication, (*iii*) ongoing transient lesions (lasting <1 week) and taking medication, (*iv*) ongoing transient lesions and not taking medication, (*v*) repetitive lesion flares, and (*vi*) poor or no response to treatment) based on lesion activity and whether or not they were taking medication. According to Murrell et al. (15), we defined the absence of lesions ($=$ no lesions) as complete remission, ongoing transient lesions as partial remission, and repetitive lesion flares and poor or no response to treatment as no remission (active). We found that patients with a mucocutaneous lesion profile had a worse "global illness activity" than those with a mucosal only lesion profile ($p=0.05$, $\tau=0.274$) (Fig. 1).

People with one autoimmune disease tend to have a higher probability to be affected by a second autoimmune disease (16–19). Our analysis showed that 61 out of 393 PV patients (15.5%) reported a co-existing autoimmune disease, with 8 of the 61 patients reporting more than one co-existing autoimmune disease (Table
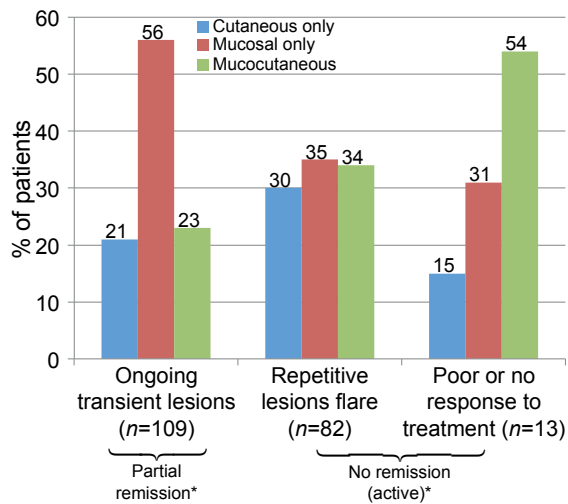
Fig. 1. Lesion location in patients with pemphigus vulgaris in relation to 3 groups of global illness activity (see text). Forty-four patients are not included in this analysis because they stated that they did not have any current lesions.

I). The occurrence of a co-existing autoimmune disease was significantly higher in females (54/61; 19.1% of all female patients) than in males (7/61; 6.3% of all male patients), $p < 0.01$.

Medical care

Twenty-three questions dealt with medical care, including current and past medications. In our study, the majority of patients ($n = 286$; 72.8%) were managed by a dermatologist for PV. Fifty-six (14.2%) patients were followed by a dermatologist and dentist, 20 (5.1%) by a family physician, 13 (3.3%) by a non-dermatology specialist, 8 (2.0%) by a dentist, 5 (1.3%) by a family physician and a dentist, and 5 (1.3%) by a non-dermatology specialist and a dentist.

Patients with PV often experience a considerable delay in diagnosis after developing symptoms (13). The delay in diagnosis from the first occurrence of lesions was <3 months for 120 patients (30.5%), 3–6 months in 131 patients (33.3%), 6–12 months in 89 patients (22.6%), and >12 months in 53 patients (13.5%). There was no significant difference in the delay in diagnosis based upon

Table I. *Co-existing autoimmune diseases. A total of 61/393 (15.5%) patients with pemphigus vulgaris (PV) reported 70 instances of coexisting autoimmune diseases. Listed below is the percent of those 61 patients reporting a specific coexisting autoimmune disease*

Autoimmune disease	PV patients affected, % ($n = 70$)
Thyroid disease	59.0
Rheumatoid arthritis	24.6
Psoriasis	13.1
Diabetes mellitus type 1	8.2
Ulcerative colitis	3.3
Vitiligo	3.3
Alopecia areata	1.6
Systemic lupus erythematosus	1.6
Myasthenia gravis	0.0

the region in the USA patients were living in (Fig. S1[1]). However, separating the groups by gender, we found a statistically significant difference between gender and delay in diagnosis (male: <3 months in 46% of patients, 3–6 months in 32% of patients, 6–12 months in 15% patients, and >12 months in 7% of patients; female: <3 months in 24% of patients, 3–6 months in 34% of patients, 6–12 months in 26% of patients, and >12 months in 16% of patients), with males more likely to be diagnosed earlier than females ($p < 0.001$, $\Lambda = 0.043$) (Fig. S3[1]).

In order to compare differing levels of treatment in patient groups distinguished by levels of disease activity, therapy status was defined according to previously published consensus definitions (15) as: no therapy, minimal therapy (defined as ≤10 mg/day of prednisone and/or 1 mg/kg/day cyclophosphamide for 12 weeks; 1.25 mg/kg/day azathioprine for 12 weeks; 10 mg/week methotrexate for 12 weeks; 1.5 gm/day mycophenolate mofetil for 12 weeks), or more than minimal therapy (anything greater than minimal therapy). Of 393 patients, 302 (76.8%) reported that they were on some type of medication, with 115/393 patients (29.3%) on minimal therapy and 187/393 patients (47.6%) on more than minimal therapy, and 91/393 patients (23.1%) were off therapy. We also found that with increasing global illness activity, therapy correspondingly progressed from no therapy to more than minimum therapy ($p < 0.001$, $\tau = 0.293$) (Fig. 2).

DISCUSSION

The IPPF is the first organization to initiate a disease registry for autoimmune bullous skin diseases. The primary phase of recruiting participants and collecting clinical data has begun, and planning for the collection of corresponding biological samples is underway.

This report is the first analysis of clinical data obtained since the initiation of the disease registry. The results are
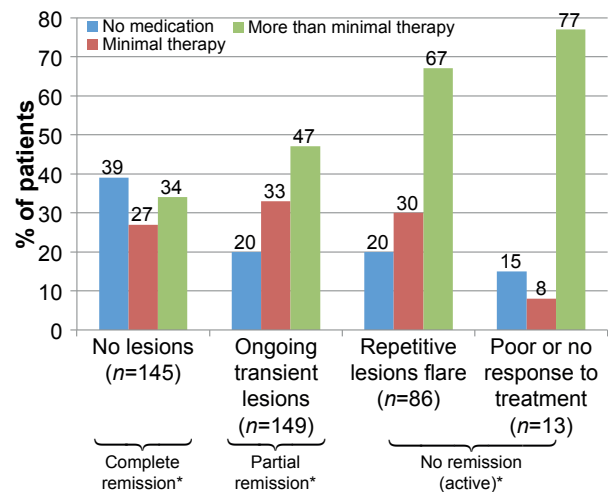

Fig. 2. Therapy regimen in relation to groups of global illness activity (for details see text).

consistent with several previously reported findings regarding PV: 1) greater female prevalence, 2) predominant onset in the 5th decade of life, 3) predominant mucosal involvement, 4) dermatologist as the primary disease manager, and 5) autoimmune comorbidity profile. Previously unreported findings revealed in this study include: 1) gender differences relating to lesion location, delay in diagnosis, and autoimmune comorbidities, 2) correlation between disease activity and level of therapy, and 3) correlation between disease activity and lesion location.

There have only been a handful of large scale (> 100 patients) epidemiologic studies of PV. Most have shown a greater female:male ratio ranging from 1.17:1 to 2.25:1 (3, 10–13, 20). To our knowledge, this study is the largest dataset in PV published to date, and shows an increased female prevalence of 2.54:1. The reasons for the female preponderance in PV (and other autoimmune diseases) remain unclear. One factor contributing to a female predominance in a disease registry such as this may relate to a potential underrepresentation of males participating in surveys, as has been previously documented (13), leading to a participation bias. It is known that women experience a more intense cellular and humoral immune response than men, perhaps rendering females more resistant to certain infections (due to a more potent response to infectious agents), but susceptible to higher rates of autoimmunity (20–22). An estrogen hormonal environment preferentially stimulates T-helper (Th) lymphocytes to secrete type 2 cytokines while androgens stimulate Th cells to produce type 1 cytokines (21, 23), which may in part also contribute to the female prevalence in a Th2-driven disease such as PV (24). However, these associations are not definitive; rheumatoid arthritis, which exhibits a greater female prevalence, is characterized by a type 1 cytokine profile, with disease being suppressed by estrogen, and disease activity diminishing during pregnancy (21, 23). Recently, increased attention is being given to the theory that microchimerism may be responsible for the female preponderance of autoimmune disease (25).

Recent studies have shown an estimated prevalence of 7.6–9.4% of the population have an autoimmune disease (19), and those individuals are at an increased risk of developing a second autoimmune disease (18). The pathogenetic mechanisms underlying the development of two or more autoimmune diseases concurrently are unknown. We surveyed patients to determine which, if any, co-existing autoimmune diseases are reported by PV patients. Overall, 15.5% of PV patients reported a co-existing autoimmune disease (mainly thyroid disease). In a study published in 2011 by our group (13), we found a similar percentage and distribution of coexisting autoimmune diseases. Another study out of Israel found a 6.3% co-existing autoimmune comorbidity in patients with PV via reporting through patients' dermatologists (26). In the present study, 88.5% of patients with a coexisting autoimmune disease were female and 11.5% were male, while the composition of the total PV patient population was 71.8% female and 28.2% male. Therefore, not only are autoimmune diseases more prevalent in women (20–22), our results suggest that polyautoimmunity is significantly more likely to be found in women. Of note, our study limited the possible response to 10 predetermined autoimmune diseases and patients were not able to input any other autoimmune conditions. Furthermore, the order in which autoimmune diseases presented was not determined. Future surveys may benefit from the inclusion of a more comprehensive list of co-existing autoimmune diseases and also from documenting the temporal sequence that multiple diseases present in individual patients. This information may be useful to help establish possible genetic and environmental links between diseases.

As in other studies (3, 11, 13), our data indicate that patients overall exhibited more mucosal lesion activity than cutaneous lesion activity. However, when patients were separated by gender, we found that males were skewed towards a more cutaneous lesion profile and females towards a more mucosal lesion profile. The reason for this difference is unclear. Autoantibody profiles, as well as environmental factors and occupational exposures, could potentially contribute to the differences in lesion profiles between genders.

A considerable delay in diagnosing PV was reported by the survey respondents. There may be a number of contributing factors. Patients may not initially have access to a dermatologist and the delay in diagnosis may be due to the lack of knowledge of this rare disease in the overall medical community. A 2008 study found that the mean wait time to see a dermatologist was greater than 30 days (27) and an official diagnosis may not be made on initial visits. Insurance may also play into an increase or decrease in diagnosis time with longer wait times, or higher refusal rates, for Medicaid insured patients compared to Medicare and private insured patients and/or insurers with low reimbursement rates (28). Of interest, we found that males had a significantly shorter delay in diagnosis than females. This seems counterintuitive, as women tend to utilize health care services greater and quicker than men (29, 30). A possible reason, based on our clinical experience, may be that women feel more comfortable with a female dermatologist and it has been shown that wait times to see female dermatologists are significantly longer than their male counterparts, sometimes more than 50% longer (28, 29). Female skewing towards a mucosal only lesional profile may also be a factor, since oral presentation of disease has been reported to delay diagnosis (31).

We observed a few discrepancies in this study that arose when cross referencing individual patients' answers to different questions. This identifies a general problem when collecting subjective data from patients,

where a lack of first hand clinical knowledge can lead to misunderstandings and confusion. To diminish such survey inconsistencies it may be helpful to conduct real time interviews with patients, or have peer health coaches (Pemphigus or Pemphigoid patients trained and /or certified in disease management) follow-up on each questionnaire. However, cost and time must be considered. An alternative approach could involve having patients' physicians or a medically trained professional fill out the questionnaire (hard copy or electronic version) with/for them.

The majority of registry participants were from the USA. Most promotional tools for the registry were directed at the local U.S. population as the IPPF, while promoting a worldwide reach, was established and is based in the USA (however all materials were available worldwide electronically and international interaction between the IPPF and patients were made when requested). Upon registering, participants were directed to a clinical survey that was available in English and Spanish languages. The internet was the major data collection tool, although paper copy questionnaires were available upon request to registry participants. Over time the IPPF plans to increase resources devoted to capturing a more global patient population for this registry.

REFERENCES

1. Pan M, Liu X, Zheng J. The pathogenic role of autoantibodies in pemphigus vulgaris. Clin Exp Dermatol 2011; 36: 703–707.
2. Tsunoda K, Ota T, Saito M, Hata T, Shimizu A, Ishiko A, et al. Pathogenic relevance of IgG and IgM antibodies against desmoglein 3 in blister formation in pemphigus vulgaris. Am J Pathol 2011; 179: 795–806.
3. Asilian A, Yoosefi A, Faghini G. Pemphigus vulgaris in Iran: epidemiology and clinical profile. Skinmed 2006; 5: 69–71.
4. Kumar KA. Incidence of pemphigus in Thrissur district, south India. Indian J Dermatol Venereol Leprol 2008; 74: 349–351.
5. Hahn-Ristic K, Rzany B, Amagai M, Brocker EB, Zillikens D. Increased incidence of pemphigus vulgaris in southern Europeans living in Germany compared with native Germans. J Eur Acad Dermatol Venereol 2002; 16: 68–71.
6. Heymann AD, Chodick G, Kramer E, Green M, Shalev V. Pemphigus variant associated with penicillin use: a case-cohort study of 363 patients from Israel. Arch Dermatol 2007; 143: 704–707.
7. Drago F, Cacciapuoti M, Basso M, Parodi A, Rebora A. Pemphigus improving with gluten-free diet. Acta Derm Venereol 2005; 85: 84–85.
8. Goldberg I, Sasson O, Brenner S. A case of phenol-related contact pemphigus. Dermatology 2001; 203: 355–356.
9. Brenner S, Tur E, Shapiro J, Ruocco V, D'Avino M, Ruocco E, et al. Pemphigus vulgaris: environmental factors. Occupational, behavioral, medical, and qualitative food frequency questionnaire. Int J Dermatol 2001; 40: 562–569.
10. Mimouni D, Bar H, Gdalevich M, Katzenelson V, David M. Pemphigus – analysis of epidemiological factors in 155 patients. J Eur Acad Dermatol Venereol 2008; 22: 1232–1235.
11. Salmanpour R, Shahkar H, Namazi MR, Rahman-Shenas MR. Epidemiology of pemphigus in south-western Iran: a 10-year retrospective study (1991–2000). Int J Dermatol 2006; 45: 103–105.
12. Michailidou EZ, Belazi MA, Markopoulos AK, Tsatsos MI, Mourellou ON, Antoniades DZ. Epidemiologic survey of pemphigus vulgaris with oral manifestations in northern Greece: retrospective study of 129 patients. Int J Dermatol 2007; 46: 356–361.
13. Gupta VK, Kelbel TE, Nguyen D, Melonakos KC, Murrell DF, Xie Y, et al. A globally available internet-based patient survey of pemphigus vulgaris: epidemiology and disease characteristics. Dermatol Clin 2011; 29: 393–404, vii–iii.
14. Anonymous. Anthropometric reference data for children and adults: United States, 2007–2010. Hyattsville, Md.: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, 2012.
15. Murrell DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, Borradori L, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. J Am Acad Dermatol 2008; 58: 1043–1046.
16. Sardu C, Cocco E, Mereu A, Massa R, Cuccu A, Marrosu MG, et al. Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. PLoS One 2012; 7: e32487.
17. Cojocaru M, Cojocaru IM, Silosi I. Multiple autoimmune syndrome. Maedica 2010; 5: 132–134.
18. Somers EC, Thomas SL, Smeeth L, Hall AJ. Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder? Am J Epidemiol 2009; 169: 749–755.
19. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun 2009; 33: 197–207.
20. Brenner S, Wohl Y. A survey of sex differences in 249 pemphigus patients and possible explanations. Skinmed 2007; 6: 163–165.
21. Gonzalez DA, Diaz BB, Rodriguez Perez Mdel C, Hernandez AG, Chico BN, de Leon AC. Sex hormones and autoimmunity. Immunol Lett 2010; 133: 6–13.
22. Ortona E, Margutti P, Matarrese P, Franconi F, Malorni W. Redox state, cell death and autoimmune diseases: a gender perspective. Autoimmun Rev 2008; 7: 579–584.
23. Walker SE. Estrogen and autoimmune disease. Clin Rev Allergy Immunol 2011; 40: 60–65.
24. Satyam A, Khandpur S, Sharma VK, Sharma A. Involvement of T(H)1/T(H)2 cytokines in the pathogenesis of autoimmune skin disease – pemphigus vulgaris. Immunol Invest 2009; 38: 498–509.
25. Gleicher N, Barad DH. Gender as risk factor for autoimmune diseases. J Autoimmun 2007; 28: 1–6.
26. Leshem YA, Katzenelson V, Yosipovitch G, David M, Mimouni D. Autoimmune diseases in patients with pemphigus and their first-degree relatives. Int J Dermatol 2011; 50: 827–831.
27. Kimball AB, Resneck JS, Jr. The US dermatology workforce: a specialty remains in shortage. J Am Acad Dermatol 2008; 59: 741–745.
28. Resneck J, Jr., Pletcher MJ, Lozano N. Medicare, Medicaid, and access to dermatologists: the effect of patient insurance on appointment access and wait times. J Am Acad Dermatol 2004; 50: 85–92.
29. Ladwig KH, Marten-Mittag B, Formanek B, Dammann G. Gender differences of symptom reporting and medical health care utilization in the German population. Eur J Epidemiol 2000; 16: 511–518.
30. Redondo-Sendino A, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. Gender differences in the utilization of health-care services among the older adult population of Spain. BMC Public Health 2006; 6: 155.
31. Sirois DA, Fatahzadeh M, Roth R, Ettlin D. Diagnostic patterns and delays in pemphigus vulgaris: experience with 99 patients. Arch Dermatol 2000; 136: 1569–1570.