Clinical Course and Factors Associated with Remission in Pemphigus Vulgaris Patients in Puerto Rico

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Objective: To describe and identify those factors associated with remission on pemphigus vulgaris (PV) patients in Puerto Rico.

Methods: This retrospective cohort study evaluated PV patients followed at the University Puerto Rico (UPR) Bullous Diseases Clinic during the 2000-2010 period. Patients included in the study had clinical and pathologic findings consistent with PV and had a disease duration of at least 3 years. Variables including gender, date of birth, time of disease onset, and date of first partial or complete remission were collected from the medical chart for each study participant. The primary outcome was to determine the number of patients who achieved partial or complete remission. Other secondary outcomes were to identify if partial/complete remission were associated to gender, disease duration, and age at onset of disease.

Results: Among 35 patients included in this study, 6 (17%) achieved complete remission and 28 (80%) achieved partial remission. A statistically-significant association was found between duration of disease and remission, predicting a 52% probability of remission after ten years of disease duration. Age at onset of disease showed a trend association with remission, although it was not statistically significant. Gender was not associated with remission.

Conclusion: These findings provide insights into the clinical course of PV and can be of value in the management and care of this patient population. [*P R Health Sci J 2012;31:14-17*]

Key words: Pemphigus vulgaris, Remission, Relapse, Puerto Rico

Pemphigus vulgaris (PV) is a rare cutaneous autoimmune disorder that manifests as flaccid blisters and erosions in the skin and mucous membranes. It is diagnosed by characteristic clinical, histopathologic, and immunologic findings. The course of the disease has significantly improved with the introduction of corticosteroids, prior to which the disease was almost invariably fatal (1-3). Even though the mortality rate is low (approximately 6%), the disease is associated with significant morbidity (1-2). Some of the complications might be secondary to immunosuppressive therapy. Thus, it is desirable to discontinue pharmacotherapeutic intervention as early as possible. Even though PV can enter remission and allow therapy discontinuation, it is difficult to predict the length of time it will take to induce remission and how long will it last once achieved (4).

There are few studies in recent years that have evaluated the clinical course and outcome of patients with PV. This study attempts to identify those factors associated with disease remission and provide insights into the course of this disease.

Methods

This retrospective cohort study was carried-out at the University of Puerto Rico (UPR) Bullous Diseases Clinic in San Juan, Puerto Rico, and was approved by the UPR Medical Sciences Campus Institutional Review Board. Participants were identified by a search of dermatology clinic records with a diagnosis of PV from 2000-2010. Patients were evaluated and diagnosed with PV by clinical, histopathologic, and/or immnologic criteria (either direct immunofluorescence (DIF)

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or serum desmoglein confirmation studies). Only patients who had disease duration of at least 3 years were included in the analysis. Partial remission was defined as a period of three or more months during which the patient was lesion free while taking systemic immunosuppressants (corticosteroids and/or adjuvant therapy). Complete remission was defined as a period of three or more months during which the patient was lesion free and was not receiving any form of systemic therapy for PV.

The following variables were collected from the medical chart for each study participant: gender, date of birth, date of disease onset, date of first partial or complete remission, therapeutic interventions and medication dosing (in particular with regards to corticosteroids) at time of remission and relapse.

The primary outcome was to determine the number of patients who achieved partial or complete remission. Other secondary outcomes were to identify if partial/complete remission or relapse were associated to specific corticosteroid dosing or other factors such as gender, disease duration, and age at disease onset.

Statistical analysis

Fisher exact test using 2-sided p values was used to determine gender difference on remission. A logistic regression model was used to determine if remission was associated to age or duration of disease. The same model was used to predict the probability of remission based on duration of disease. Analyses were performed using SPSS software, version 18.

Results

Characteristics of the study population

Out of 67 patients followed at the UPR Bullous Diseases Clinic between 2000 and 2010 for PV, 35 patients met the inclusion criteria (Figure 1). The characteristics of all study participants are listed in Table 1. The distribution of male and female sex among the study sample was 51% and 49%, respectively. The mean age at onset was 48 years, with a range of 27-73 years, and a standard deviation of 12 years. The mean disease duration at the time of evaluation was 5.6 years, with a range of 3-16 years, and standard deviation of 3 years.

The majority (54%) of patients experienced both skin and mucosal involvement, 29% had only oral lesions, and 17% had only cutaneous lesions. Among those with cutaneous lesions, the trunk was the most commonly affected area (54%), followed by the face (51%). There were no reported deaths.

Twenty-nine (83%) patients were treated with a combination of systemic corticosteroids and adjuvant therapy (defined as one or more of the following: mycophenolate mofetil, azathioprine, dapsone, tetracyclines, methotrexate, rituximab, and intravenous immunoglobulin). Fourteen percent were treated with only systemic corticosteroids and one patient (3%) with only adjuvant therapy (dapsone). Dapsone was the most common adjuvant therapy employed followed by tetracyclines. Fifty-one percent of patients had one or more hospitalizations. Of these patients, 50% were admitted for intravenous immunoglobulin administration, 44% for high-dose prednisone, and 6% for intravenous antibiotics (Table 1).

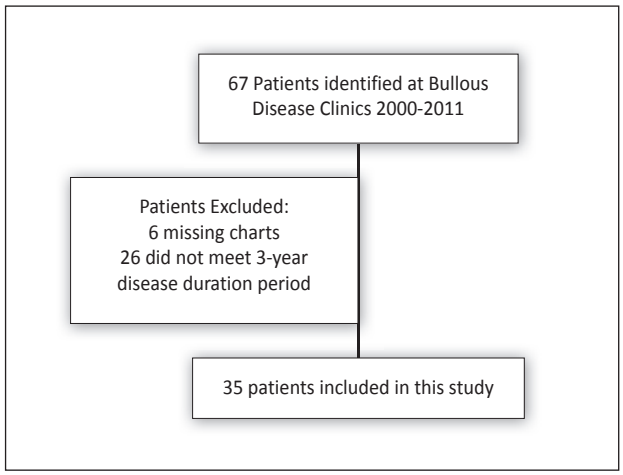

Figure 1. Flow of participants identified at the Bullous Diseases Clinics in 2000-2010 with a diagnosis of pemphigus vulgaris.

Table 1. Characteristics of study participants (n=35)

Gender, n (%) male	18 (51%)
Mean age at onset, years (range)	48 (27-73)
Mean disease duration, years (range)	5.6 (3-16)
Body areas affected, n (%)	
Oral lesions only	10 (29)
Mucocutaneous	19 (54)
Cutaneous only	6 (17)
Trunk	19 (54)
Face	18 (51)
Scalp	11 (31)
Arms	8 (23)
Legs	7 (20)
Other	
Generalized involvement	1 (11%)
Genitalia	1 (11%)
Number of deaths	0
Number (%) of patients treated only with systemic steroids	5 (14%)
Number (%) of patients treated with adjuvant therapy only	1 (3%)
Number (%) of patients treated with adjuvant therapy and systemic steroids	29 (83%)
Number (%)of hospitalized patients	18 (51%)
Medications administered during hospitalization, n (%)	
Intravenous immunoglobulin	9 (50%)
Prednisone	8 (44%)
Intravenous antibiotics	1 (6%)

Remission

Among the 35 patients included in this study, 28 (80%) experienced partial remission and 6 (17%) had complete remission. One patient failed to achieve partial or complete remission during the study period. We could not identify a pattern of specific corticosteroid dosing associated to partial remission. Similarly, we analyzed if there was a pattern between specific corticosteroid dosing and the first time a patient experienced a disease relapse after partial remission (data available for 11 patients). No consistent trend was identified. Furthermore, corticosteroid dosing among individual patients at the time of relapse evolved throughout time.

Medication regime and complete remission

All patients who achieved complete remission (n=6) had been treated with corticosteroids, half of which were also treated with adjuvant therapy (consisting of azathioprine and dapsone). Sixty-six percent (n=4) were hospitalized during the course of their illness; all of them were admitted for high-dose prednisone therapy.

Factors associated with complete remission

A Fisher's exact test was conducted to determine if gender was associated with complete remission, however, the results were not statistically significant (p=0.4) (Table 2). A logistic regression model was used to determine if disease duration and age at onset were associated with complete remission. The analysis revealed an odds ratio of 1.62 (p=0.02) and 1.09 (p=0.08) for disease duration and age at onset, respectively. We used the same model to predict the probability of remission based on disease duration, showing that at 10 years of duration there was a 52% probability of complete remission (Figure 2).

Table 2. Association of complete remission with gender, disease duration, and age at disease onset

	All patients (n=35)	Complete remission (n=6)	No complete remission (n=29)	Odds Ratio	*p* value
Male sex, n	18	2	16	n/a	0.40*
Disease duration, years	5.6	9.75	4.74	1.62	0.02**
Age at disease onset, years	48	56.5	46.17	1.09	0.08**

*By Fisher's Exact Test; **By Logistic Regression

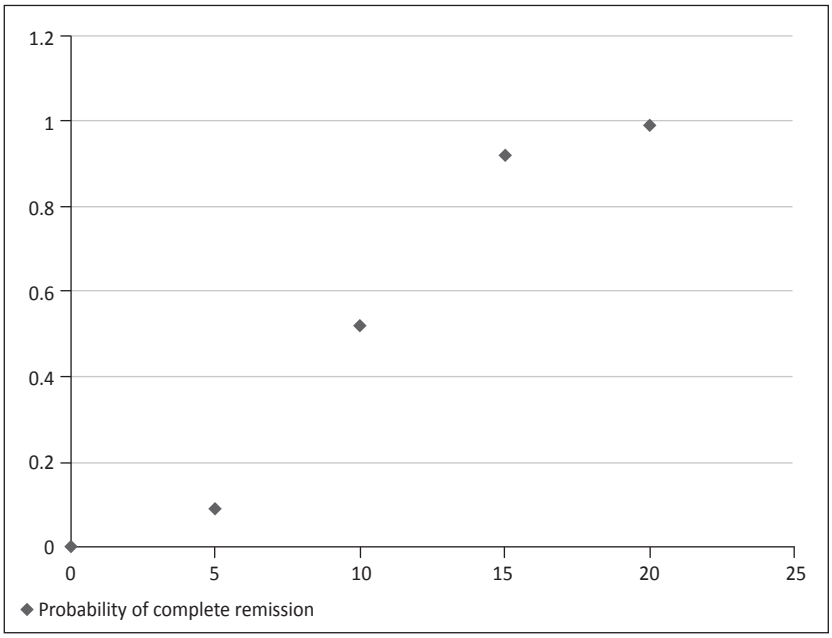

Figure 2. Probability of remission (y-axis) based on disease duration (x-axis). Duration is provided in years.

Discussion

There is a vast amount of medical literature regarding treatment options for PV but few articles address the clinical course of the disease. Previous studies have reported an average age of onset of 40-57 years (5-7). In our study, the average age of onset was 48 years.

When comparing our findings to other studies, it seems that different definitions to the word "remission," have been employed in the past (8-9). Some authors define a complete remission as absence of skin lesions without treatment; however, the period of time for which it is sustained frequently varies across studies or at times are not even specified. In a study by Herbst and Bystryn, the authors defined complete remission as a period of more than one month during which the patient was receiving no systemic therapy and was lesion free (4) We understand that perhaps one month is not enough time to observe a pattern of disease behavior (activity or inactivity) and thus decided to define our remission period as three or more months. Further complicating things, some studies utilize disease response/improvement as an outcome measure. Given the significant variability of markers of disease severity and clinical classification among studies, it is almost impossible to draw comparisons across different analyses. Further randomized controlled trials with standardized methodology and outcome measures are needed in the future.

Previous studies have reported partial and complete remission rates of 70-89% and 9.7-28.9% , respectively (4, 6, 7,

10). These rates are similar to the findings in our study, where 80% of patients achieved partial remission and 17% achieved complete remission. The patients were able to sustain complete remission for an average of 3 years. This is comparable to previously reported complete remission duration of 2.5 years (5).

So far, there is no consensus or uniformly accepted therapeutic ladder for medication regime and dosing in PV (11). In our study, most patients achieving partial remission were treated with a combination of prednisone and adjuvant therapy, in particular dapsone. Corticosteroids were the mainstay of the treatment regime in all patients achieving a complete remission. They were accompanied by dapsone or azathioprine in half of those achieving complete remission. This finding reaffirms the important role played by corticosteroids in the management of PV. Corticosteroid dosing varied significantly within patients achieving partial remission and within those experiencing relapse, further emphasizing the importance of an individually tailored approach to therapy.

In our analysis, the patient population achieving complete remission had longer disease duration of 9.75 years at the time of evaluation (versus 4.74 years in those not achieving complete remission). This association was found to be statistically significant. Furthermore, disease duration can be viewed as a predictor of probability of complete remission. This is not surprising, as previous reports have also observed that incidence of remission increases with time (4). Additional factors found to be associated with remission in other studies include disease severity at time of diagnosis (the less severe the more likely to remit) and early response to therapy (4).

There are several limitations in this study. The retrospective nature of the study and incomplete documentation found upon medical chart review limited the amount of clinical data available for analysis. In particular, we could not evaluate other characteristics such as level of disease severity as a prognostic factor for remission or identify any particular trends with regards to particular corticosteroid dosing and remission or relapse. Future prospective studies with standardized progress notes that include detailed intensity scores should be helpful with this regard. The small sample size, although comparable to previous PV studies, limits the ability to detect differences between groups.

In conclusion, remission in PV, whether partial or complete, can be achieved in most patients. Complete remission occurs in less than a fourth of patients and its probability increases as a function of disease duration. These findings provide insights into the clinical course of PV and can be of value in the future management and care of this patient population.

Resumen

Objetivo: Describir e identificar factores asociados a remisión en pacientes con pénfigo vulgar (PV) en Puerto Rico. Métodos: En este estudio de cohorte retrospectivo se evaluaron pacientes con PV seguidos en las Clínicas de Enfermedades Ampollosas de la Universidad de Puerto Rico durante el período de 2000-2010. Los pacientes incluidos tenían hallazgos clínicos y patológicos consistentes con PV y una duración de enfermedad de más de 3 años. En la revisión de expedientes se recopilaron variables tales como sexo, fecha de nacimiento, fecha de comienzo de enfermedad, fecha de primera remisión parcial o completa. El objetivo principal fue determinar el número de pacientes que lograron remisión parcial o completa. Otros objetivos incluyeron identificar si la remisión parcial o completa estaba asociada a sexo, duración de la enfermedad, o edad al comienzo de la condición. Resultados: De los 35 pacientes incluidos en este estudio, 6 (17%) lograron una remisión completa y 28 (80%) una remisión parcial. Se encontró una asociación estadísticamente significativa entre la duración de la enfermedad y remisión, prediciendo una probabilidad de 52% de remisión después de 10 anos de duración de la enfermedad. La edad al comienzo de la enfermedad demostró una asociación con remisión, aunque no fue estadísticamente significativa. El sexo no mostró ninguna asociación a remisión. Conclusión: Estos hallazgos proveen un mejor entendimiento del curso clínico de PV y puede ser de utilidad en el manejo futuro de estos pacientes.

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