Original Article

A Clinical Profile and Co-morbidities of Pemphigus Vulgaris Patients: A Study of 35 Cases

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Abstract

Background: *Pemphigus vulgaris (PV), an autoimmune blistering disease involving the skin and mucosa. PV frequently begins with oral lesions and progresses to skin lesions. Autoimmune bullous skin disorders are associated with IgG or IgA auto- antibodies against distinct adhesion molecules of the epidermis and dermal epidermal basement membrane zone, respectively. These auto- antibodies lead to a loss of skin adhesion which shows up clinically as the formation of blisters or erosions.* ***Objectives:*** *To characterize the clinical parameters and co-morbidities of PV patients from a single tertiary medical centre in Bangladesh.* ***Material and Methods:*** *This observational study was done including 35 PV patients attending in the department of Dermatology and Venereology, Khwaja Yunus Ali Medical College Khawja Eunus Ali Medical College from 2010 to 2014. Thirty patients of pemphigus diagnosed clinically confirmed and treated over a 4-year period (2010-2014).* ***Results:*** *Majority of the patients 45.7% belongs to age group 41-50 years. Mean age 47.12±11.13. The male to female ratio in our study sample was 1:1.5. The youngest patient was 17 years old and the oldest 68. For both genders, the risk of onset peaked during the fifth and sixth decade of life. Out of 35 patients, 15(42.9%) was presented with mucosal lesions only, while 13 patients 37.1% had mucocutaneous lesions and 7 patients 20% had only cutaneous lesions. The most common comorbidies were hypertension 20.0%, osteoporosis 17.1%, and diabetes 8.6%, thyroid disease 8.6%, psoriasis 5.7%, rheumatoid arthritis 2.7%, rheumatic fever 2.9%, autoimmune hepatitis 2.9%, and myasthenia gravis 2.9%.* ***Conclusion:*** *The associated comorbidities of PV emphasize the need for dermatologists to keep a high index of suspicion and actively evaluate patients to determine their presence.*

Key words: *Bullous disease, Comorbidity, Pemphigus Vulgaris.*

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Introduction

Pemphigus is a rare, potentially life-threatening, autoimmune blistering disease involving the skin and mucosa. In pemphigus vulgaris (PV), the most common form of pemphigus, IgG autoantibodies target desmogleins, which are part of the desmosome complex. The functional inhibition of desmosomes by autoantibodies results in loss of cell-to-cell adhesion and intra-epidermal blister formation, which is the clinical hallmark of the disease. Owing to the relative rarity of the disease, only a limited number of studies are available. Nevertheless, studies from different parts of the world demonstrate differences in the characteristics of the disease.[1]

Pemphigus vulgaris (PV) frequently begins with oral lesions and progresses to skin lesions. Autoimmune bullous skin disorders are associated with IgG or IgA auto- antibodies against distinct adhesion molecules of the epidermis and dermal epidermal basement membrane zone, respectively. These auto- antibodies lead to a loss of skin adhesion which shows up clinically as the formation of blisters or erosions. In pemphigus, loss of adhesion occurs within the epidermis while in the pemphigoids, linear IgA dermatosis, epidermolysis bullosa acquisita and dermatitis herpetiformis, loss of adhesion takes place within or underneath the basement membrane zone. The auto-antigens of these disorders are largely identified and characterized.[1,2]

The diagnosis of autoimmune bullous skin diseases is based on histology and direct immunofluorescence of perilesional skin and the serological detection of auto antibodies by

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indirect immunofluorescence and recombinant autoantigens.[3] Two major variants of pemphigus is identified by the level of cleavage within the epidermis, by different clinical pattern and by the auto antibodies. Suprabasal clefting is seen in pemphigus vulgaris (PV) and its variants pemphigus vegetans. Most superficial subcorneal bullae are formed in pemphigus foleaceus (PF) and pemphigus erythematosus (PF) and presented as superficial blisters on the seborrheic areas of the body. In addition there may be paraneoplastic pemphigus, drug induced pemphigus, IgA pemphigus.[1,4] The aim of this study was to evaluate the clinical presentation of pemphigus group of patients attending in the tertiary care hospital.

Materials and Methods

PV who were either admitted to the Department of Dermatology or visited the outpatient department between 2010 and 2014. Diagnoses were based on: (i) appearance of mucosal and/or cutaneous involvement that was clinically compatible with PV (blisters or erosions); (ii) histopathology showing suprabasal acantholysis in the epidermis; and (iii) direct immunofluorescence demonstrating IgG intercellular deposition throughout the epidermis pattern. Patients with other forms of pemphigus disease besides PV (pemphigus folliaceus or IgA pemphigus), as well as those with equivocal diagnosis, were excluded. Age at diagnosis, sex, site of initial lesion, associated illness at diagnosis. The study was approved by the institutional ethical committee. Data were analysed by the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA) version 22.0 for Windows. Normally distributed numerical data was summarised by its mean values and standard deviation and categorical data was presented as frequency and Percentage.

Results

Table I: Distribution of the study patients by age, sex and initial site of lesions among PV patients (n=35)

Variables	Frequency	Percentage (%)
Age (in years)		
<20	1	2.9
21-30	2	5.7
31-40	5	14.3
41-50	7	20.0
51-60	16	45.7
>60	4	11.4
Mean±SD	47.12±11.13	
Sex		
Male	14	40.0
Female	21	60.0
Male : Female ratio	1:1.5	
Initial lesions		
Mucous membrane	15	42.9
Skin	7	20.0
Mucocutaneous	13	37.1

Majority of patients (45.7%) belongs to age group 41-50 years. Mean age 47.12±11.13. The male to female ratio in our study was 1:1.5. The youngest patient was 17 years old and the oldest 68. For both genders, the risk of onset peaked during the fifth and sixth decade of life. Out of 35 patients, 15(42.9%) was presented with mucosal lesions only, while 13 patients (37.1%) had mucocutaneous lesions and 7 patients (20%) had only cutaneous lesions.

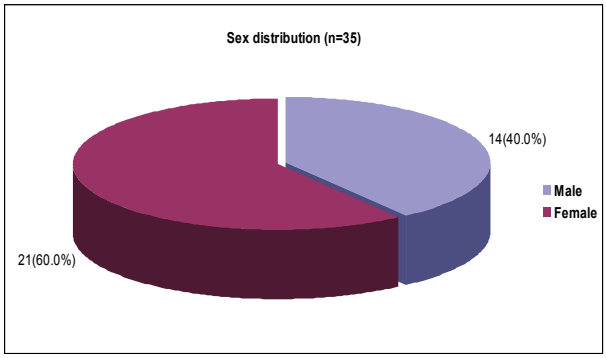

Figure 1: Pie diagram showing the sex distribution of the patients

Figure showed 21(60%) patients were male and 14(40.0%) patients were female. The male to female ratio in our study was 1:1.5.

Table II: Distribution of the PV patients by co-morbidities (n=35)

Co-morbidities	Frequency	Percentage (%)
Hypertension	7	20.0
Osteoporosis	6	17.1
Diabetes mellitus	5	14.3
Hyperlipidemia	3	8.6
Thyroid disease	3	8.6
Psoriasis	2	5.7
Ischemic heart disease	2	5.7
Rheumatoid arthritis	2	5.7
Asthma	2	5.7
Rheumatoid fever	1	2.9
Autoimmune hepatitis	1	2.9
Myasthenia gravis	1	2.9

Table 2 showed the comorbidities, as documented at the time of PV diagnosis. The most common comorbidities were hypertension (20.0%), osteoporosis (17.1%), and diabetes (8.6%), thyroid disease (8.6%), psoriasis (5.7%), rheumatoid arthritis (2.7%), rheumatic fever (2.9%), autoimmune hepatitis (2.9%), and myasthenia gravis (2.9%).

Discussion

PV, the most common variant of pemphigus, is an autoimmune disease with a well-established autoimmune basis. Our results showed that the average age at the onset of disease was 47.12±11.13 years. In consistent, Mimouni et al.[5] reported an average age of 53.5 years in 155. Khondker reported mean age of onset of pemphigus was 41.5 years.[6] Asilian et al.[7] reported among the patients of pemphigus the mean age of onset was 56.1 ± 9.7 years, ranging from 36 to 68 years. In European countries8, PV usually develops at an older age, as shown by

studies from Sicily, Italy 56 years, Finland 57.5 years, the UK median age of 71 years, and Croatia 53 years. A younger age at onset was reported in Kuwait 36.5, Iran mean age of 38 in one study and 43 in another, Saudi Arabia 43.1, China 44 and Brazil 41.5. In general, age at onset appears to be higher in northern European countries compared to Middle Eastern, Asian, and African countries. It is not clear, however, whether this observation stems from variations in population age distributions among countries due to different birth rates and life expectancy or represents substantial, geo-epidemiological changes in PV characteristics. These differences may result, for example, from different genetic susceptibilities and/or exposure to different environmental risk factors. They may also reflect the accessibility of medical services for patients, resulting in diagnosis of mild cases and a better registry.

Female predominance in many autoimmune diseases is well established[9] and is especially remarkable for certain diseases, including thyroiditis/hypothyroidism female:male [F:M] ratio of 18:1, Sjogren's syndrome 9-15:1, systemic sclerosis 12:1, and systemic lupus erythematosus 9:1. Several theories have been proposed to explain this gender difference in the prevalence of autoimmune diseases including PV. Genetic factors, specifically genes encoded on the X chromosome, direct hormonal influence of oestrogens, and environmental factors which may also be, in part, sex- specific have been suggested as possible contributors for this gender skewing of autoimmune diseases.[10] A female predominance was also found in our study F:M; 1.5:1, as well as in previous studies[8,11,12] Iran, Turkey, South Africa, Japan, and most European countries. However, a reversed male:female ratio has been reported in other countries.[13-15] In Saudi Arabia, males outnumber females M:F; 2.2:1 and male predominance occurs in China, Kuwait, Bangladesh and Spain. The reason for this large gender disparity among PV patients around the world is not known, and additional large-scale studies are needed to address this subject.

It is generally accepted that autoimmune diseases tend to co-exist in certain patients as part of a general autoimmune diathesis.[16] In this regard, PV has been associated with other autoimmune diseases, including thyroid disease, myasthenia gravis, Sjogren's syndrome, and rheumatoid arthritis. In our study, 3 patients 8.6% had thyroid disease. Previous case series of thyroid disease in pemphigus patients have reported conflicting results of either no increased rate of autoimmune thyroid disease17 or an association.[18-19] Similarly, Leshem et al.[20] reported a prevalence rate of 3.6% of thyroid disease among pemphigus patients. In the current study, 2.8% of the patients had psoriasis, 1% had rheumatoid arthritis, 0.7% had rheumatoid fever, and 0.3% had autoimmune hepatitis and myasthenia gravis. The prevalence of autoimmune diseases among PV patients reported here is in good agreement with that reported by Leshem et al.[20] but lower than that reported by others.[21]

Soon after diagnosis, all PV patients in our study underwent a routine evaluation by an endocrinologist to determine bone mineral density. Osteoporosis was diagnosed at this stage in a relatively high number of patients 6 patients 17.1%. In a previous retrospective case control study by Wohl et al.[22], a significant association between pemphigus and osteoporosis was identified, in which 40.4% of 255 pemphigus patients had osteoporosis compared with 6.5% of 509 controls $p<0.001$; this was more pronounced in males and younger patients. This association persisted after controlling for confounders, including age, sex, and duration of glucocorticosteroid therapy.

The morphological forms of PV have been described, based on clinical and anti-desmoglein antibody profiles, as mucosal dominant type or mucocutaneous type[23] In most PV patients, the lesions tend to appear first in the oral mucosa and then spread to the skin, representing the epitope-spreading cascade.[24] In our study, data regarding the initial site of presentation was 42.9% presented with mucosal lesions only, 37.1% presented with mucocutaneous lesions, and 20% had only skin lesions. A wide variation in the initial clinical presentation is found among different countries. In a survey of 393 PV patients from around the world.[21] 65.9% reported a history of mucocutaneous lesions, followed by those with mucosal lesions only 22.5%, and those with a history of cutaneous lesions only 11.6%. Isolated initial cutaneous involvement was reported in 12% of PV patients[25] and 4.9% of Turkish patients11 but in 21% of non-North American PV patients. The reason for the wide variation in clinical presentation at onset between different studies is not known. It is possible that genetic and environmental factors favour the production of a distinct anti-desmoglein antibody profile with the resultant typical phenotype. In the current study, no mortality during the follow-up period.

Conclusion

The age at onset of PV in Bangladesh was generally lower than in European countries, but higher than in Middle Eastern and other Asian countries. There was female predominance for PV. Our results do not representation of whole over the country. We believe that these findings merit further investigation. These findings emphasize the need for the dermatologist, who is often the main physician of the pemphigus patient, to keep a high index of suspicion and actively evaluate PV patients for the presence of these comorbidities.

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