CLINICO-EPIDEMIOLOGIC PROFILE AND TREATMENT OUTCOMES OF PEMPHIGUS VULGARIS: A STUDY IN A TERTIARY CARE CENTER

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Abstract:

Background: *Pemphigus vulgaris is an autoimmune, potentially fatal vesiculobullous disease of skin and mucous membranes. The clinical profile and epidemiologic characteristics varies in patients to patients and in different communities. The aim of this study was to evaluate the clinical and epidemiological features, morbidity and mortality of pemphigus vulgaris and to compare that with other studies of different communities.*

Methods: *It was an observational study, conducted on 24 hospital admitted cases of pemphigus vulgaris at the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The duration of the study was from November 2018 to February 2020. Patients who were confirmed as pemphigus vulgaris both histopathologically and direct immunofluroscent test were included for that study.*

Findings: *The mean age (SD) of the patients was 47(15.5) years. Male outnumbered female in that study and male to female ratio was 1.4: 1. The mean (SD) duration of disease was 15(18.6) months. Pain (70.8) was the commonest symptoms. Trunk (92%) was the commonest cutaneous site of involvement followed by oral mucosa (71%). Oral prednisone was the mainstay of treatment and it was given to 24 (100%) of the patients. The immunosuppressant adjuvant was given in 79% cases. Azathioprine (62.5%) was the commonest of them. To avoid osteoporosis calcium supplement with or without vitamin D and bisphosphonate was given in 92% cases. The mean (SD) hospital stay was 5.4(3.3) weeks. Bacterial infection was the commonest complication and it was found in 2 patients. The mortality rate of that study was 4.16%.*

Conclusion: *pemphigus vulgaris is a dermatological emergency and the maximum patients need hospitalization for proper care. Hospital acquired infections are the common complication and that may leads to septicemia and death. To decrease the mortality of pemphigus vulgaris the care givers have to be more watchful about the potential of infections.*

Keywords: *Pemphigus vulgaris, Immunobullous disease, Prednisolone, Adjuvant therapy.*

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Introduction:

Pemphigus vulgaris (PV) is an autoimmune disease that characterized by presence of blisters on cutaneous and mucosal surfaces. The various genetic and environmental factors leading to development of pemphigus vulgaris. Several environmental factors may triggers the disease including medications, trauma, infections, UV exposure or other radiation injury.[1] Pemphigus is derived from the Greek word “pemphix” the meaning of that word was blister.

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Pemphigus was first described in the year 1788 by Stephen Dickson, who found a patient with a blister on her tongue.[2] There are several variants of pemphigus disease such as: pemphigus vulgaris (PV), Pemphigus foliaceus (PF), paraneoplastic pemphigus, pemphigus vegetans, pemphigus erythematosus, IgA pemphigus and drug-induced pemphigus. PV is the most common typical and well-characterized variant of them. Pemphigus and pemphigoid result from deposition of autoreactive antibodies directed against various intraepithelial and subepidermal proteins, resulting in the formation of bullae or erosions.[3, 4] PV is a rare disease the incidence rate of that disease is variable in different community. The incidence rate was 4.4/million/year in Kerala India, 1.6/million/year in France and that was 6.7/million/year in Tunisia.[5]

The pathogenesis of PV was first described and established by Beutner and Jordon in 1964. They conducted indirect immunofluorescent (IIF) test with the serum of PV patients and found that antibodies was attached to the surface of keratinocytes of stratum spinosum. The authors observed that the reactive antigen was present only on the surface of stratified squamous epithelium.[6]

The targeted antigens in PV is the calcium-dependent intercellular adhesion proteins desmoglein (DsG 1) 1 and desmoglein 3 (DsG 3). The desmogleins are members of the cadherin protein family and they act as anchoring keratin intermediate filaments on the cell membrane of keratinocytes.[7]

The clinical manifestations of pemphigus vulgaris (PV) are determined according to the profile of autoantibodies. The type of desmoglein affected has clinical importance. The location of PV lesions depends on the specific desmoglein targeted by the autoreactive antibodies.[8] DSG1 is usually found within superficial layers of the epidermis. In contrast, Dsg3 is more common within the as mucosal surfaces.[9] Antibodies to Dsg3 being associated with mucosal dominant pemphigus vulgaris, whereas the presence of both anti-Dsg3 and anti-Dsg 1 is associated with mucocutaneous pemphigus and with lesions both in the oral cavity and on the skin.[10]

There are two major forms of pemphigus, pemphigus vulgaris (PV), in which auto-antibodies against Dsg3 and Dsg1 lead to mucosal and skin involvement, and in pemphigus foliaceus (PF) the autoantibodies against Dsg1 lead to superficial skin lesions only. PV is further subdivided in two major subtypes based on their site and immunological profiles: mucosal PV (mPV), in which anti Dsg3 autoantibodies causes the mucosal disease, and both anti Dsg1 and anti Dsg3 are responsible for mucocutaneous PV (mcPV).[11] Pemphigus vulgaris is a dermatological emergency condition and moderate to severe cases need hospitalization. Proper treatment planning and management of complication is the key point to subside the mortality rate of PV. Present study was aimed to find out the common epidemiological and clinical features and risk factors of admitted patients of a tertiary care hospital and the advanced management plan which could be helpful for dermatologists and other healthcare professionals. There is scarcity of study like that on PV in our community.

Materials and Methods:

This was a prospective cohort single centered study conducted on patients who were admitted at Dermatology ward of Bangabandhu Sheikh Mujib Medical University, Dhaka. The study duration was from November 2018 to February 2020. The COVID-19 pandemic had stopped that study to a further progression. Patients who were diagnosed with pemphigus vulgaris and included in that study had to fulfill the following criteria: i) clinically the patient had to present with flaccid bullae or with denuded skin area after rupture the bullae ii) in histopathology they must had intraepidermal suprabasal acantholysis and iii) in direct immuno-fluorescent (DIF) test their slide must had IgG and or C3 deposition at the surface of epidermal keratinocytes. Details socio-demographic characteristics, medical history and thorough clinical examination was done and recorded in a preformed data collection sheet. Duration of disease, presenting symptoms, site of lesions, risk factors, treatment profile, complications, morbidity and mortality was observed and was recorded accordingly. With informed written consent of patients all data was collected and

preserved in a secured computer device. Collected data were analyzed with the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA) version 23.0 for Windows. Normally distributed numerical data was summarized by its mean values and standard deviation and categorical data was presented as frequency (n) and percentage (%). Analyzed data was presented with text and tables.

For every patients the aim and procedure of the study was clarified in easy understandable language before taking consent and assured them that their personal information would not be disclosed to any person or any media. Ethical issues was maintained according to Helsinki declaration.

Results:

An observational study on 24 diagnosed cases of pemphigus vulgaris was conducted at the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Table I showed the demographic and clinical information of patients. Mean age(SD) of patients was 47(15.5) years. Maximum patients was in 50-59 years age group. Male patients outnumbered the female. The male to female ratio was 1.4: 1. Presenting symptoms were pain, burning, itching or mixed in cases. Pain was the major symptom but other two symptoms were presented by around half of them.

Majority of the patients were presented with lesions on trunk (91.66%) and involvement of oral mucosa was the next common site (70.83%). The other site of involvement were as above distribution. Mean (SD) duration of disease was 15(18.6) months. Among the cases half (50%) of them had been suffering for 1 year. Majority of patients (54%) was admitted with their first attack of pemphigus vulgaris rest of them were with relapse.

Regarding comorbidity and risk factors 25% patients were obese, 21% was hypertensive, 17% was diabetic, 21% was smokers and 8% was alcoholic.

Table I

Demographic and clinical information

Trait	Frequency /figure	Percentage
Demography		
Age		
Age group (years)		
20-29	3	12.5
30-39	6	25.5
40-49	3	12.5
50-59	9	37.5
60-69	1	4.2
70-79	1	4.2
80-89	1	4.2
Mean age **±SD years**	47**±15.47**	
Age range (years)	65	
Min-Max (years)	20-85	
Sex		
Male	14	58.67
Female	10	41.33
Ratio (Male:Female)	1.4:1	
Comorbidity/Risk factors		
Hypertension	5	20.83
Diabetes	4	16.66
Obesity/ Over weight	6	25
Smoking	5	20.83
Alcohol	2	8.33
Presenting symptoms		
Pain	17	70.83
Itching	12	50
Burning	13	54.16
All 3 of above	10	41.66
Site of lesion		
Oral mucosa	17	70.83
Eye	3	12.5
Nasal mucosa	3	12.5
Genitalia	1	4.16
Anal mucosa	5	20.83
Trunk	22	91.66
Upper limb	14	58.33
Lower limb	12	41.66
Head, neck and face	14	58.33
Duration of the disease		
Duration groups (months)		
0-12	12	50
13-24	5	20.83
25-36	3	12.5
>36	4	16.66
Mean duration (month) & SD		15±18.6
First attack or relapse		
First attack	13	54.16
First relapse	6	25
Second relapse	4	16.66
Third relapse	1	4.16

Table II

Treatment profile, hospital stay time and complication of patients

Trait	Frequency	Percentage
Treatment profile		
Systemic corticosteroid	24	100
Topical Silver Sulfadiazine	14	62.5
Azathioprine	15	62.5
Methotrexate	2	8.33
Mycophenolate mofetil	1	4.16
Rituximab	1	4.16
Oral antibiotic	16	66.66
Oral Calcium supplement	22	91.66
Hospital stay time (week)		
0-4	4	16.66
5-8	17	70.83
9-12	3	12.5
Mean duration and SD	5.42±3.26	
Complications of patients		
Bacterial infection	2	8.33
Oropharyngeal candidiasis	1	4.16
Septicemia	1	4.16
Corneal ulcer	1	4.16
Death	1	4.16

Oral prednisolone was the main stay of treatment all of the cases was treated with that. Adjuvant was given in 79% cases among them Azathioprine was the major option (62.5%). To avoid osteoporosis calcium supplement was given in 92% cases. Other treatment option was as above distribution. Mean(SD) hospital stay of patients was 5.42(3.3) weeks. Maximum of cases had stayed at hospital (71%) in 5-8 weeks group.

Complications that developed in cases during hospital stay was as above distribution. Bacterial infection, candidiasis, septicemia and corneal ulcer was the listed complication of pemphigus vulgaris patients. In our study period one (4.16%) patient died with septicemia followed by multi-organ failure. Rest of them were improved.

Discussion:

The age of participants were from 20 years to 85 years. Mean age of them was 47 ± 15.47 years. Maximum patients was in 50-59 years age group. In a similar study conducted in India in 2016 the authors found the mean age PV patients was 50.06 ±15.45 years and their maximum patients were in (47%) 41-60 years age group.[12] Razzaque MA et. al in their study on 35 patients of PV found that mean age of cases was 47.12 ± 11.13 years and maximum participants (45.7%) were in 51-60 years age group.[13]That two studies were almost similar with our findings regarding the age.

In current study male participants were more than female. The male to female ratio was 1.4: 1. The involvement of male and female cases are variables in different study of PV. Female outnumbered male in two different studies. Chowdhury J et al. found male to female ratio in pemphigus was 1: 1.9 and that was 1: 1.5 in other study.[12,13]

Mean duration of disease was 15 ±18.6 months or 1.25 years. Half of the patients had developed PV within 1 year. Mean age onset of disease was calculated 45.75 years. More than half of the patients admitted at hospital with their first attack. Rest of them had admitted with relapse.

Usually PV patients need hospitalization at their moderate to severe stage of disease. Roughly when body surface area (BSA) involvement become 10% or more. In a study with 32 pemphigus patients in 2016 the authors found that mean duration of PV was 8.56 ±20.17 months and mean age of onset of PV was 50.78 years.[12] That findings is comparable with our study.

Pain was the commonest presenting symptom. Pain was presented on lesional skin, eyes, perineum and other affected site. Itching and burning were the next two common features. Usually we have a common belief that itching is the symptom of bullous pemphigoid and pain is for PV. Zeidler C, et al. found that burning (83.1%) was the most common symptom in patients of PV, pain (68.4%) and itching (47.5%) were the next two common types.[14] In that two studies around half of PV cases were presented with itching so we think that itching should be kept in consideration as a presenting symptom of pemphigus vulgaris along with pain and burning.

Kilic A, mentioned about burning and painful sensation after rupture of bullae and in erosive areas of skin. He also added epistaxis and hoarseness of voice while mucosal erosion present.[15]

Trunk was the commonest site of cutaneous involvement and oral mucosa was the next common site. In PV patients 71% were muco-cutaneous type and 29% was cutaneous type but no one found pure mucous type. In a study with 31 patients of PV the authors found that 67.7% cases were mucocutaneous type, 22.5% were mucosal type and 9.7% cases were cutaneous type.[16] Razzaque MA et al. in an observational study described that 37% of PV cases were mucocutaneous type, 20% were cutaneous type and 22.5% cases were pure mucosal type.[13] Their findings were comparable with our results.

In almost all cases of PV treatment was started with an empirical oral antibiotic and a topical silver sulfadiazine. The mainstay of treatment was oral corticosteroid. For all 24 patients oral prednisolone 2 mg/Kg body weight was the starting dose after baseline evaluation. On consideration the long time adverse effect like osteoporosis 22 (92%) patients was given the calcium supplements but 2 of them who had GIT intolerance. Among the cases 79% was given adjuvant therapy. Azathioprine was the commonest adjuvant used and others was methotrexate, Mycophenolate mofetil and Rituximab.

In a similarly designed study in Morocco, 83.8% patients were treated with corticosteroid monotherapy. They had used oral prednisolone at a dose of 1–1.5 mg/kg in 74% patients, 1–2 mg/kg in 19.4% and >2 mg/kg in 5.6% cases. That dose was used 1-2 mg/Kg/day in Tunisia and 30-120 mg/day in Kuwait. They used pulse methylprednisolone IV in few severe cases.[16,17] In those studies they used oral prednisolone as a first line treatment like our study and dose was within the range of 2mg/kg/day that was also similar with us. The use of adjuvant was less similar with our hospital admitted cases. In Morocco the authors had administered immunosuppressive adjuvant in 5 (16.1%) patients among them 4 cases with Azathioprine 1 cases with methotrexate. They had administered Rituximab in 1 patients who was refractory to first line therapy and the outcome was better. Azathioprine was the first choice of adjuvant also in Tunisia (100-150 mg/day) and in Kuwait (1-3 mg/Kg/day).[16,17] The pattern of treatment of PV with corticosteroid dose and adjuvant selection is similar with our study but they use some other adjuvants like cyclosporine, Dapsone and cyclophosphamide which was not used in our hospital.

Mean hospital stay of PV patients was almost 38 days. Patients had leaved hospital when the condition improved or due to personal causes. Among the cases 21% patients developed major complication and need extra treatment support. Bacterial infection was the commonest of them other complications was oropharyngeal candidiasis, corneal ulcer and septicemia. The mortality rate of our study was 4.16%. A female patient of 32 years had developed septicemia and died on 3rd week of her hospital admission. The mortality rate of PV was found 4.8% in a study on 148 PV patients in Turkey. In their study period (1998-2004) total 5 PV patients had died 3 of them with septicemia, 1 with

myocardial infarction and 1 with unknown cause.[18] In another study on 159 hospital admitted PV patients in Croatia from 1980 to 1998 the mortality rate was 8.8 % and their causes of death were sepsis and cardiopulmonary failure.[19] The disease outcome was revolutionized by the introduction of corticosteroids in 1950s which decreased mortality rate from 77% to 30%. The disease mortality rate reduced to about 6% with the proper use of various adjuvant treatments.[20] The mortality rate of pemphigus vulgaris the above studies were similar with our results.

Confirmation of diagnosis of PV by direct immunofluroscent test, baseline latent TB screening (IGRA test), bone mineral density (BMD) scanning for osteoporosis assessment, blood culture and skin and mucous membrane culture for infections and experiences of use adjuvant all that facilities are the strong weapon to minimize morbidity and mortality level to a reasonable level that only available in tertiary care hospital. All that findings could improves the management skill of dermatologists of district and general hospital.

Limitation of current study was that the prognosis and follow up of patients was not done due to COVID-19 pandemic. We recommend a large scale multi-centric study to strengthen the present study outcomes.

Conclusion:

Pemphigus vulgaris is a dermatological emergency and most of the time the patient needs hospitalization. In previous days around the year 1950 before introduction of corticosteroid the mortality rate of PV was very high. Proper dose of corticosteroid and selection of adjuvant therapy has downgraded this rate in a satisfactory level. To control the hospital acquired infections and proper monitoring will be best weapon to reduce the morbidity and mortality of pemphigus vulgaris at a further extent.

Conflict of interest:

Nothing to disclose

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