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A PRELIMINARY STUDY ON CLINICAL OUTCOME OF CORTICOSTEROID THERAPY IN PEMPHIGUS PATIENTS

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Abstract

Introduction: Pemphigus is life threating blistering of autoimmune disease of the skin and mucous membrane characterised by autoantibodies (auto ABs) against desmoglein-3 (DSG-3). Desmosomal adhesions, protein expressed on the surface of epidermal keratinocytes.
Aim: The present study was to assess the incidence rate of pemphigus, to evaluate the clinical course along with clinical manifestations, Complications and Metabolic factors of patients with pemphigus and to investigate the disease severity and induction of remission during the clinical course and whereas to assess the oxidative stress and antioxidant status in pemphigus patients in our hospital.
Material and Methods: A prospective study was conducted over a period of January 2012 to December 2012 at dermatology department, MGM Hospital, Warangal. The data was collected from 32 cases of Pemphigus on the basis of Age, Sex, Social Habits, BMI, Histopathological forms, Clinical manifestations and Drug therapy. This hospital is 1200 bedded government hospital provided Outpatient and Inpatient care for Indian citizen especially in Telangana region free of cost.
Results: Of the 32 pemphigus patients, 75% were diagnosed with Pemphigus Vulgaris (PV), 12.5% with Pemphigus Foliaceus (PF) and 12.5% with Bullous Pemphigoid (BP). The male to female ratio was approximately 1:1.3. The mean age of onset was 40.8 years in Pemphigus patients. The Onset of disease was 29.85. 34% of patients with Pemphigus had both the mucosal and skin involvement during the clinical course while 25% at the onset of disease. The most common complication was found to be increase blood sugar (40%). Most commonly prescribed adjuvant is dapsone. Majority attained the complete remission and remaining of them attains partial remission. Oxidative stress levels were higher and antioxidant status levels were lower in study subjects when compared to controls.
Conclusions: PV is the most common subtype of Pemphigus in our Hospital and usually affects females more than males. Our study reveals that mucosal and skin involvement is common. Corticosteroids and dapsone as adjuvant is majorly prescribed. Most of patients attain complete remission and remaining of them achieves partial remission. Oxidative stress levels were higher and antioxidant status levels were lower in our study subjects when compared to controls.

Key words: Clinical course; Pemphigus; Remission; Treatment

Introduction

Pemphigus is an uncommon disease with an incidence rate ranging 0.5-3.2/100,000/year. The peak incidence of pemphigus vulgaris occurs between the fourth and sixth decades of life with a male-to-female ratio of 1:2 [1]. The prevalence of disease in various countries are United states (32%), Jews (16.1%), Greek (9.3%), Bulgarian (4.7%), Malaysian (2%), Saudi Arabian (1.6%). Epidemiology of pemphigus has shown different trend in India compared with Western literature in various counts. The incidence of pemphigus among the dermatology outpatient attendees has varied widely, 0.09 to 1.8% [2]. The incidence assessed by clinic-based questionnaire survey conducted in Thrissur district, Kerala, was 4.4 per million per year. The incidence was found to be higher than available data from Germany, France, and lower than Tunisia [3].

Therefore, the aim of present study to assess the incidence rate of pemphigus and to evaluate the clinical course along with clinical manifestations, Complications and Metabolic factors of patients with pemphigus. In additon to that to investigate the disease severity and induction of remission during the clinical course and to assess the oxidative stress and antioxidant status in pemphigus patients in a tertiary care hospital.

Materials and Methods

The present study was conducted at the department of Dermatology of a tertiary care teaching hospital, i.e., Mahatma Gandhi Memorial Hospital, Warangal, Andhra Pradesh, India, which is 1200 Bedded multidisciplinary Tertiary Care government hospital. The study was carried out for the period of one year. The patients included in the study who was suffering with Pemphigus. Sample/ Data collection was performed according to hospital regulations after approval by the Hospital administration / Ethical committee. The study was conducted in various steps.

Step 1: Identify or selection of Patient inclusion in the study.

All patients diagnosed pemphigus on the basis of history, skin biopsy report of the patient along with the clinical features like fluid filled lesions, multiple hyperpigmented lesions all over the body and "Nikolsky sign" were included in our study. All subjects attendee completed a detailed standardized questionary. The victims were also sorted for different epidemiological factors like age, gender, marital status, socio-economic status and life style pattern. All patients were reviewed and admitted in dermatology department based on severity of disease. The treatment included with corticosteroids, emollients (liquid paraffin), multivitamin tablet and dapsone.

Step 2: Design of the study.

Study period: The study was planned to be carried out for a period of one year consent from the hospital authority. The Protocol of the study which includes the Introduction, Objective and Methodology was submitted to the Superintendent of our hospital and to Kakatiya Medical College to obtain the Ethical Committee approval and was obtained to carry out the present study.

Step 3: Defining criteria, Standards and Design of Data Entry Format Inclusion Criteria.

Patients with Pemphigus undergoing prednisolone treatment of Age ≥ 20, either sex.
Exclusion Criteria:
- Patients without Pemphigus
- Patients with Pityriasis versicolor, Eczema, Candida infections

Step 4: Literature Survey.

The literature supporting the study was collected and analysed. The different sources used to collect the literature were Micromedex drug information databases, various websites like PubMed, Dove Press, Science alert, Bentham Publisher, Pharmaintelligence, Journal on Web, Science direct, DOAJ, Medline, etc.

Step 5: Data collection.

Data were recorded in a case record form that was particularly designed for this study. Data concerning age of onset, sex, presenting symptoms, characteristic of skin and mucosal lesions, laboratory investigations, treatment outcomes and clinical course were obtained.

Step 6: Sample Collection.

Five (5ml) venous blood samples were collected from the patients after obtaining the Informed consent form from the patient or the attendee. The samples were collected in 5ml EDTA vials (for serum) and 5ml heparin tubes (for plasma). The samples were immediately transferred to the cooling centrifuged at 6000 rpm for 20 minutes. The supernatant was separated into a labelled eppendroff's tubes and kept at 40ºC till biochemical analysis. The amount of lipid peroxidation products present in the serum samples were estimated by the Thiobarbituric acid reactive substances (TBARS) method [4]. The Glutathione is endogenous antioxidant; it forms a coloured complex with DTNB, which is measured spectrophotometrically [5,6]. For the estimation of total antioxidant status, we used a stable free radical- diphenyl-picryl hydrazyl (DPPH) at the concentration of 0.2mM in methanol [7,8].

Disease severity and remissions of Pemphigus

Disease severity was classified according to the severity scale created by Herbst and Bystryn. The scale is based on the compilation of the extent of disease and the intensity of therapy. The extent of disease was classified by the number of body areas involved, including scalp, face/neck, upper trunk, lower trunk, arms, legs, oral mucosa and genitals. A score 0 was given for no lesions, ½ for lesions healed within 48 hours, 1 for 1 site involved, 2 for 2 to 3 sites involved, 3 for 4 to 5 sites involved and 4 for ≥ 6 sites involved. The score for the intensity of therapy was given as follows: 0 for no treatment required, ½ for only topical treatment needed, and 1, 2, 3 and 4 for ≤ 15, 16 to 49, 50 to 89 and ≥ 90mg of Prednisolone (or equivalent) per day respectively. If ≤ 100 mg/day of azathioprine or cyclophosphamide or gold or dapsone or cyclosporine was used, an additional score of 1 was added. An extra score of 2 was added if > 100 mg/day of azathioprine/cyclophosphamide or plasmapheresis were used. Then the sums of these scores of $\leq 2+$, 3 to 6+ and $\geq 7+$ were used to classify the disease as mild, moderate and severe disease respectively. Complete remission was defined as a period of more than 1 month during which the patient was receiving no systemic therapy and was lesion free. Partial remission was defined as a period greater than 1 month during which the patient was lesion free and receiving no more than 15 mg/day if prednisone or its equivalent, receiving only 100 mg/day or less of cyclophosphamide or azathioprine, or receiving only gold or dapsone. Duration of remission was classified as short if it was at least 1 month but less than 6 months in duration and was classified as long if it lasted 6 months or longer.

Statistical analysis

Statistical analysis was carried by student t-test using Graph Pad Prism Version-5. Results were expressed in Mean±SD. Probability values of $P < 0.05$ were considered to be statistically significant. t-test: The t-test was performed to compare the average of biochemical parameters.

Results

In this study, total 32 patients were diagnosed with Pemphigus. Out of them 14 were male and 18 were female. Ratio of men to women is 1:1.3.

Table I shows the mean age limit of cases was found to be 40.81±13.72. Whereas, control was found to be 43.91±11.52. Of 32 cases onset of disease < 1 year includes 22% of patients, 1-4 years includes 47%, 5-8 years includes 31%. The greater mean value of age was 23.29±3.208 and it was found to be 41-50 years.

Gender	Number of Patients (n=32)	Percentage (%)
Male	14	44
Female	18	56
Total	32	100
Onset of diseases	08	04
<1	10	22
1-4	15	47
5-8	07	31
Age and BMI of study subjects	Mean value of BMI	Standard Deviation
Below 30	21.31	4.430
31-40	20.93	3.851
41-50	23.29	3.208
51-60	22.90	3.746
Above 60	24.20	2.828
Age in years	Control (n=32)	Case (n=32)
Below 30	07	07
31-40	05	11
41-50	12	08
51-60	06	04
Above 60	02	02

Table I. Patient characteristic of pemphigus in our study population.

The prevalence of pemphigus among study subjects shows, 75% of patients had Pemphigus Vulgaris, 12.5% of had Pemphigus Foliaceus and 12.5% had Bullous Pemphigoid are shown in Table II.

The clinical manifestation of study subjects show vesicle/bullae 100%, 81% erythematous base, 66% normal skin base, 53% patch/plaque, 88% erosion/ulcer, 13% pustules and remaining 13% show scar as morphology of skin lesions respectively as shown in Table III.

Type of Pemphigus	Number of Patients (n=32)	Mean value of age
Pemphigus Vulgaris	24	40.29±12.78
Pemphigus Foliaceus	04	31.50±10.91
Bullous Pemphigoid	04	53.25±15.78

Table II. Prevalence of Pemphigus among study subjects.

Morphology of skin lesions	Number of Patients (n)	Mean value of age
Vesicle/bullae	32 (100%)	40.29±12.78
Base: Erythematous base	26 (81%)	31.50±10.91
Normal skin base	21 (66%)	53.25±15.78
Patch/plaque	17 (53%)	
Erosion/ulcer	28 (88%)	
Pustule	04 (13%)	
Scar	04 (13%)	

Table III. Clinical manifestations of study subjects.

Among 32 patients, 1 patient had lesions beginning on the oral mucosa at the onset of disease and 1 of them still show only oral mucosal involvement during the follow-up period (pure oral pemphigus). 23 patients had lesions beginning on the skin at the onset of disease and 20 of them still show skin involvement during the follow-up period, remaining 8 of them had both mucosal and skin involvement at the onset of disease and 11 of them still show both during the follow-up period as shown in Table IV.

Site of involvement	At onset	During clinical course
Oral mucosa	01 (3%)	01(3%)
Skin involvement	23 (72%)	20 (63%)
Both oral mucosa and skin	08 (25%)	11 (34%)

Table IV. Site of involvement at onset and during clinical course.

Biochemical factors	Mean value ± SD	'P' value
ESR (mm)	33.75±20.91	
RBS (mg/dl)	129.3±39.83	
B. Urea (mg/dl)	28.06±5.73	<0.0001
S. Creatinine (mg/dl)	0.887±0.21	
Hb (gm %)	11.02±1.18	

Table V. Biochemical profile of study subjects.

The mean values of Biochemical factors such as ESR, RBS, B.Urea, S.Creatinine and Hb were estimated. *P (<0.0001)* was statistically significant (Table V).

Of 32 pemphigus patients, Anemia was the most common side effect found (56%), followed Hyperglycemia (40%), Infection (3%), Weight gain (31%). Serious infection associated with mortality occurred in 1 patient (3%) of PV as shown in Table VI and were treated with high dose corticosteroid and had been admitted to the hospital. During the hospital stay, he later developed septic shock which resulted in death.

Complications	Number of Patients
Hyperglycemia	13 (40%)
Infection	01 (3%)
Weight gain	10 (31%)
Anemia	18 (56%)
Death	01 (3%)

Table VI. Associated complications of study subjects.

Distribution of lesions in subjects	Number of patients (%)
Mouth	34
Trunk	65
Face	68
Upper extremities	78
Lower extremities	78
Genital	28
Scalp	46

Table VII. Associated complications of study subjects.

The extent of disease is more in Upper and Lower extremities (78%), followed by Face (68%), Trunk (65%), Scalp (46%), Mouth (34%) and Genital (28%) as shown in above Table VII. Among 32 patients, 75% of patients treated with systemic steroids, 9% of patients treated with adjuvant, 13% with both adjuvant and steroids and 3% of them treated with topical medications was represented above Table VIII.

Among the study patients, none of them show mild severity, 23 (72%) patients moderate severity of disease and 9 (28%) patients show severe as shown in Table IX.

Treatment	Number of Patients
Systemic Steroids	24 (75%)
Adjuvant	03 (9%)
Adjuvant and Steroids	04 (13%)
Topical Medications	01 (3%)

Table VIII. Intensity of therapy in study subjects.

Disease severity	Number of Patients (%)
Mild	Nil
Moderate	23 (72)
Severe	09 (28)

Table IX. Disease severity of study subjects.

Table X shown relation between initial disease severity response to treatment and induction of remissions of study subjects.

Two factors were found to be predictive of remission induction: disease severity at the time of diagnosis and an early response to therapy as shown in Table XI. Patients with moderate disease at onset manifested by a severity score of 6 or less were twice as likely to have complete remission as those with severe disease (severity score of ≥7). Patients with a rapid response to therapy were twice as likely to have a complete remission than those who did not, regardless of the patient's initial disease severity (ie, complete remission in 75% compared with 40% of patients with moderate disease and in 33% compared with 17% of those with severe disease).

Levels of MDA, a major oxidation product of peroxidised polyunsaturated fatty acids, have been considered as an important indicator of lipid peroxidation was presented in Table XII.

Disease Severity at Onset	Number of Patients	Number (%) with Complete remission
Mild	Nil	Nil
Moderate	23	12 (52)
Severe	09	02 (22)

Table X. Relation between initial disease severity response to treatment and induction of remissions of study subjects.

Rapid Responders		Slow Responder	
Number of Patients	Number (%) with Complete Remission	Number of Patients	Number (%) with Complete Remission
Nil	Nil	Nil	Nil
08	06 (75)	15	06 (40)
03	01 (33)	06	01 (17)

Table XI. Rapid responders vs slow responder.

Parameter	Case	Control	'P' value
MDA (µ mol/ml)	17.95±10.48	17.71±5.22	<0.0001
GSH (µg/ml)	24.20±22.24	37.98±10.08	<0.0001
TAS (nmol/ml)	31.86±13.37	38.23±10.50	<0.0001

Table XII. Levels of MDA, a major oxidation product of peroxidised polyunsaturated fatty acids, have been considered as an important indicator of lipid peroxidation.

Discussion

Pemphigus has a variety of epidemiological profiles in different regions of the world. This was the preliminary study done by us in Telangana region. Our study reveals that PV is the most common subtype of pemphigus. Our data show that pemphigus affected females more than males. Male to female ratios is 1:1.3 which is similar to Ameneh Yazdanfar [9]. In our study, the mean age of onset was in the fifth decade of life which is similar to the previous studies of Piamphongsant et al. [10] (mean age = 40.8 years). The Onset of disease ranged from <1 to 8 years and the mean duration of pemphigus was found to be 29.85±25.97 which is similar to Yu-Huei Huang et al [11]. The mean BMI was 22.05±3.72.

The nature and distribution of the lesions as well as mucosal involvement seen in different types of Pemphigus in our study was similar to b. Flaccid bullae/vesicle were seen in all cases. Patients with Pemphigus often have mucosal and skin involvement. In our study, 34% of patients with Pemphigus had both the mucosal and skin involvement during the clinical course while 25% had skin and mucosal lesions present at the onset of disease which is similar to the results reported by Chams Davatchi et al [12]. Approximately half of patients with Pemphigus in our study had the eroded lesions as clinical manifestations. Our study also showed the Mean values of ESR, RBS, B.urea, S.creatinine and Hb%.

In our study disease severity was showed to be moderate and

similar to Kanokvalai Kulthanan et al [13]. Corticosteroids are the major drugs used in pemphigus patients because are able to reduce autoantibody levels and also dramatically decrease the mortality rate. Nevertheless, high dose administration and prolonged usage of corticosteroids may bring about serious complications in our study. Most common complication was increase blood sugar after using corticosteroids and anaemia, which was seen in 40% and 56% of the patients. The mortality rate in our study was 3% (1 patient) which is similar to Ameneh Yazdanfar [9]. In our study 75% of patients with Pemphigus received prednisolone. Adjuvant drugs were additionally prescribed to 13% of patients to achieve disease control. The advantages of adjuvant drugs are the steroid-sparing effect and the augmentation of steroid efficacy. The most common prescribed adjunctive drug in our centre was dapsone. 9% patients with pemphigus treated with dapsone monotherapy and achieved remission and 13% patients treated with dapsone concurrently with prednisolone which is similar to Gurcan et al. analysed 55 pemphigus patients treated with dapsone from the literature published between 1969 and 2008. They state that 86% of PV patients and 78% of PF patients responded to treatment either with dapsone alone or dapsone concurrently with prednisolone.

The other parameter commonly used to judge response to therapy in pemphigus is the induction of a remission.

Review of all major studies of pemphigus conducted during the past 4 decades describes these as occurring fewer than one-third of patients the average incidence of remissions in the more recent studies is similar to the results reported in earlier studies. The proportion of evaluable patients in complete remission was 33% and 75% respectively. The remaining patients were in partial remissions controlled with only an adjuvant which is similar to Andrew Herbst et al [8].

In pemphigus, the increased production of reactive oxygen species from activated neutrophils decreases concentrations of antioxidant vitamins and enzymes in plasma and red blood cells (RBC), resulting in oxidative stress. We compared lipid peroxidation, a measure of reactive oxygen species production, total antioxidant status, reduced glutathione (GSH). Lipid peroxidation levels (malonyldialdehyde) were significantly higher ($p < 0.0001$) in Pemphigus patients than in control subjects. Significantly lower concentrations of total antioxidant status $p< 0.0001$) and reduced glutathione levels ($p < 0.0001$) were found in Pemphigus patients when compared to controls is similar to the Naziroğlu M et al. showed Plasma and RBC lipid peroxidation levels (malonyl dialdehyde) were significantly higher ($p<0.05$) in pemphigus vulgaris patients than in control subjects.

Conclusion

The present study is the first to reveal the incidence, clinical manifestations, complications, metabolic factors, management and clinical course of Pemphigus patients in tertiary care hospital. In our study we found that Pemphigus is the most common form and affects females more often than males meanwhile our study reveals that mucosal and skin involvement is common in Pemphigus patients, whereas, Corticosteroids are majorly prescribed to study subjects and dapsone is the most common adjuvant drug prescribed. The majority of patients attain complete remission and remaining of them achieves partial remission. In addition to that Oxidative stress seems to be responsible for the onset/aggravation of many disease conditions. It is considered as one of the factor for the etiopathogenesis of Pemphigus. The oxidative stress levels in study subjects were found to be higher when compared to controls and antioxidant status levels were found to be lower in study subjects when compared to controls.

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