

A Retrospective Study of Pemphigus in a Tertiary Care Centre in South India

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ABSTRACT

BACKGROUND

Pemphigus is a group of rare, life-threatening autoimmune bullous diseases of the skin and mucosa which result in intraepidermal blistering. Associated autoimmune conditions and the extensive mucocutaneous detachment impair the quality of life. Immunosuppressive treatment adds to the morbidity in patients. We wanted to assess the clinical presentation of pemphigus among the study subjects along with the outcome of pemphigus patients with the extent of the disease and results of pus culture.

METHODS

Retrospective analysis of case records of patients with pemphigus in a tertiary care hospital during a period of 3 years was done in 2015. Demographic data, clinical findings, underlying medical disorders, details of deaths, investigation reports and treatment details were recorded.

RESULTS

Common age group affected was 51-60 years (31.5 %) among a total of 54 pemphigus patients. There were 26 males and 28 (51.9 %) females and in majority of the patients (44.4 %) duration was less than 6 months. Out of 47 patients, oral mucosal involvement was grade 1 in 20 (37 %) cases, grade 2 in 12 (22.2 %) and in 15 (27.8 %) patients it was grade 3. Histopathological examination showed suprabasal cleft in 82.1 %, subcorneal blister in 5.7 %, acantholytic cells in 48.6 % and row of tombstone appearance in 9.4 %. Out of 36 patients, DIF test reported intercellular IgG in 65 % and C3 in 50 %. Diabetes was found in 14 (25.9 %), candidiasis in 12 (22.2 %), thyroid disease in 6 (11.1 %) and hypertension in 3 patients. Three patients died. Among 10 patients with more than 30 % body surface area involvement, 1 (10 %) patient died. Two (13 %) deaths occurred among 15 patients in whom pus C&S was positive.

CONCLUSIONS

Pemphigus patients were of slightly higher (51 - 70 years) age group and the 3 patients died were females. Autoimmune disorders like diabetes and thyroid disorders were found among many patients and their family members. Infection could be an important cause of death, but no statistically significant association was found in the present study.

KEYWORDS

Pemphigus, Steroids, Comorbidity, Deaths

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BACKGROUND

Pemphigus is a chronic autoimmune bullous disease, mediated by autoantibodies against desmosomal glycoproteins on the surface of keratinocytes of the squamous stratified epithelia. These autoantibodies directed against adhesion molecules cause separation of epidermal keratinocytes resulting in intraepidermal bullae. It is characterised by widespread denudation of skin and mucous membranes and is associated with considerable morbidity.¹ There are mainly two types of pemphigus, pemphigus vulgaris- PV (its variant pemphigus vegetans), and pemphigus foliaceus- PF (variant pemphigus erythematosus- PE). Genetic and immunological factors are well established in the etiopathogenesis of pemphigus. Pemphigus vulgaris (PV) is characterised by formation of flaccid blisters over trunk, scalp and extremities. Oral erosions are present almost always and can affect quality of life. Contrary to this, usually there are no oral lesions in pemphigus foliaceus. In PF, characteristic lesions are crusted plaques and scaling over seborrheic areas. Pemphigus vulgaris the commonest type is usually a disease of the middle aged can be associated with other autoimmune conditions like thyroid disease and Rheumatoid arthritis.

Apart from clinical examination, diagnosis is aided by Tzanck smear examination, skin biopsy for histopathology examination and immunofluorescence studies. In the past, mortality rate was high among untreated pemphigus patients. Prognosis of pemphigus has improved since the introduction of corticosteroids and it remains the mainstay of treatment. Immunosuppressive therapy has reduced the mortality rate to 5 - 10 %. Steroid sparing agents like Methotrexate, Azathioprine, Cyclophosphamide, Mycophenolate mofetil or biologicals such as Rituximab need to be added, mainly due to the side effects of the steroids required to induce or maintain remission of pemphigus. Drugs can be withdrawn once complete remission of the disease is attained. Patients must be kept under follow up as relapses may occur.

However, pemphigus is still a life- threatening disease despite treatment using corticosteroids and other immunosuppressive drugs. Major cause of death is septicaemia and electrolyte imbalance. The prognostic factors of the disease include the advanced age of the patient, the extent of skin and mucosal involvement and the presence of infections.²

Objectives

1. To assess the clinical presentation of pemphigus among the study subjects.
2. To assess the outcome of pemphigus patients with the extent of the disease and results of culture and sensitivity from the lesions.

METHODS

A retrospective study of pemphigus patients from a tertiary care hospital in the Department of Dermatology in Kerala

was planned and human ethical committee approval (IEC.No.06/19/2014/MCT) was obtained in 2014. The study population included clinically and investigation proven cases of pemphigus. Case records of hospitalized patients for a period of 3 years (January 2012- December 2014) was collected in 2015 from the medical records library.

Demographic data, clinical findings, underlying medical disorders, details of deaths, investigation reports and treatment details of the patients were entered in a proforma. Severity of skin involvement was assessed based on the involved body surface area (BSA). Oral mucosal involvement was graded depending on the number of sites affected as grade 1, 2 and 3.

Statistical Analysis

Data was analysed using SPSS software. The Fisher's exact test was used to find out the association of severity and pus culture reports with the outcome as the sample size was small. Confidence rate higher than 95 % was considered as significant ($P < 0.05$).

RESULTS

Medical records of 54 pemphigus patients were studied. Common age group affected was 51 - 60 years- 17 patients (31.5 %) and the next group being 61 - 70 years- 13 patients (24.1 %) as shown in Figure - 1. Thus majority (55.6 %) of the pemphigus patients were in the age group 51 - 70 years - 30 patients. Twelve patients (22.2 %) were in the age group 31-50 years. The patients comprised of 26 males (48.1 %) and 28 (51.9 %) female patients (Table - 1). Nineteen (35.2 %) patients were house-wives, 15 (27.8 %) were manual labourers and 9 (16.7 %) were skilled workers. Forty five (79.6 %) patients were married (Table -2). Twenty four (44.4%) patients were having high school education and only 2 were illiterate as shown in Figure -2. Majority (81.5 %) of the patients were non-smokers.

Majority of the patients (44.4 %) presented within 6 months and 11 patients (20.4 %) in 7-12 months of the disease. The duration of the disease was more than 2 years in 8 (14.8 %) patients. Presenting symptoms were pain (33.3 %), pruritus (16.7 %) and both pain and itching in 6 (11.1 %) cases. In 28 (51.9 %) patients, onset was on skin, 23 had on mucosa and both skin and mucosa in 3 patients. Anterior chest wall (18.5 %) was the common site of onset on skin and on scalp in 4 patients. History of atopy was present in 6 patients and malignancy in 2 cases. Family history of diabetes was found in 17 patients, malignancy in 4, vesiculobullous diseases in 3, thyroid disorders in 2 and vitiligo in one patient.

Both vesicles and bullae were the primary lesions in 24 (44.4 %), and either vesicles in 22.2 % or bullae in 13 % patients. Frequency of various areas affected include upper trunk in 76.4 %, limbs in 74.6 %, scalp in 52.1 %, lower trunk in 50.4 % and face in 44.8 % patients. Body surface area (BSA) of involved skin could be assessed in 33 patients. The extent was less than 10 % in 4 (7.4 %), 11-30 % BSA in 19 (35.2 %) and more than 30 % in 10 (18.5 %) patients.

In 47 patients, grading of oral mucosal involvement was done. It was grade 1 in 20 (37 %) cases, grade 2 in 12 (22.2 %) and in 15 (27.8 %) patients grade 3 involvement. Oral lesions were present in 85.3 % patients, genital lesions in 22.3 %, and nasal lesions in 14.9 % patients.

Extent of the disease was severe in 10 patients. Among these 10 patients, eight had moderate to severe grading of oral involvement and in seven patients other mucosae were involved. Among 19 patients with moderate skin involvement, 8 patients were having oral mucosa with grade 2 or 3. Other mucosal involvement was found in seven cases. Out of 4 cases with mild extent of the disease, one patient showed involvement of mucosa other than oral mucosa. Out of 15 cases with severe (grade 3) oral mucosal involvement, 8 (14.8 %) were females and 5 had involvement of other mucosa. Extent of the body surface area was moderate to severe in 29 cases. Only 18 (33.3 %) patients had some nail changes.

In Tzanck smear, acantholytic cells were found in 55.6 %, neutrophils in 22.3 %, eosinophils in 16.7 % and lymphocytes in 11.1 % among 36 patients. Skin biopsy for histopathological examination was done in 48 cases. It reported suprabasal cleft in 82.1 %, subcorneal blister in 5.7 %, acantholytic cells in 48.6 % and row of tombstone appearance in 9.4 %. Intercellular IgG was seen in 65 % and 50 % showed C3 among 36 patients in whom DIF was done. Pus culture isolated staphylococcus aureus in 7 (13 %) patients, Methicillin resistant staphylococcus aureus (MRSA) in 7 (13 %) and streptococci in 1 (1.9 %) patient. There were 51 (94.4 %) PV, 3 PF and no pemphigus vegetans or PE patients. Steroids alone was given for 34 (63 %) patients. Other immunosuppressants used included Dexamethasone- cyclophosphamide pulse (DCP) therapy, Methotrexate and Azathioprine. They were advocated in 20 patients. Comorbidities observed were diabetes in 14 (25.9 %), candidiasis in 12 (22.2 %), thyroid disease in 6 (11.1 %) and hypertension in 3 (5.6 %) patients.

Out of 54 pemphigus patients, 3 (5.6 %) died. Among 27 patents above 60 years, 2 (6.1 %) died and the other one (4.8 %) was above 60 years of age. Three (11 %) among 28 females died. Among 24 patients with less than 6 months duration of the disease, 2 (8.3 %) died and in the third patient the duration was more than 1 year. Among 10 patients with more than 30 % BSA involvement, 1 (10 %) died. Pemphigus severity index score was not recorded in these case sheets. And all the 3 deaths (7.7 %) occurred among 36 patients with mild or moderate degree of oral mucosal involvement (Table - 3). But this was not found as statistically significant. Among the deaths, two had mucosal onset and one with onset of the lesions on skin.

Another finding was that, out of 15 patients where pus C&S was positive, 2 (13 %) patients died (Table - 4). Out of the 3 cases died, one patient was treated with steroids alone and the other 2 were given other immunosuppressants like Cyclophosphamide, Methotrexate or Azathioprine also. Two deaths (6.9 %) were noted among 29 patients having comorbidities. Two patients were diabetic and one showed candidiasis among the 3 patients who died. One patient died due to severe thrombocytopenia (platelet count - 12,000) and in another patient the cause of death was septicaemia

(MRSA) and multiorgan dysfunction. The third patient died of cardiopulmonary arrest. She was found as ANA positive and MRSA was cultured from her skin swab.

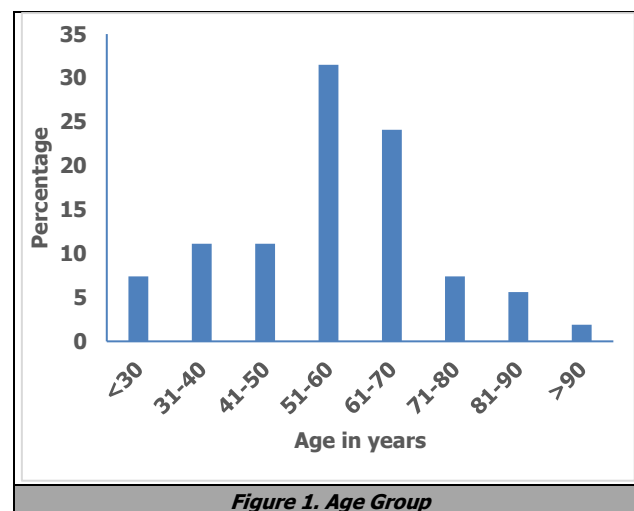


Figure 1. Age Group

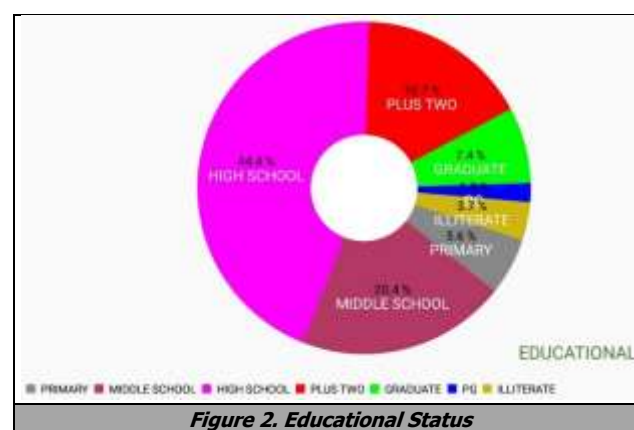


Figure 2. Educational Status

Gender	Frequency	Percent
Male	26	48.1
Female	28	51.9
Total	54	100

Table 1. Gender

Marital Status	Frequency	Percent
Unmarried	9	16.7
Married	43	79.6
Widow	1	1.9
Separated	1	1.9
Total	54	100

Table 2. Marital Status

Grading	Outcome		Death		Total		p
	n	%	n	%	n	%	
≤2	36	92.3	3	7.7	39	100	0.552
>2	15	100.0	0	0.0	15	100	
Total	51	94.4	3	5.6	54	100	

Table 3. Grading

*Fisher's exact test - p < 0.05

Pus C&S	Outcome		Death		Total		p
	n	%	n	%	n	%	
Positive	13	86.7	2	13.3	15	100	0.142
Negative	24	100.0	0	0.0	24	100	
Total	37	94.9	2	5.1	39	100	

Table 4. Pus Culture & Sensitivity

*Fisher's exact test

DISCUSSION

The retrospective study included 54 patients. Majority of the pemphigus patients were in the age group 51- 70 years- 55.6 % (61 - 70 years- 24.1 %). Patients in the age group 41-50 years were only 11.1 %, probably because they were having milder disease and were not admitted in the hospital. Pemphigus among the higher age group of 40- 59 years was also reported by Kandan et al.³ However, in a study conducted by Varala S et al,⁴ majority were in the age group of 30–40 years. In the present study, females constituted 51.9 % of cases and males 48. 1 %. In contrast, Parmar D et al observed the disease mainly among men (70.8 %).⁵

Pain was the presenting symptom in 33.3 % patients in the present study. Out of 50 cases, 10 (20 %) presented with pruritus and 20(40 %) with pain and burning sensation in the study by Huda et al.⁶ In the present study, vesicles and bullae were present in 44.4 % and 35.2 % had either vesicles or bullae as primary lesion. Contrary to this, all the 31 pemphigus cases had either vesicle or bullae as the primary lesion in a study done in Karnataka (Kudligi C et al).⁷

In the present study, extent of the disease was severe in 10 patients and one of them died. Among these 10 patients, eight had moderate to severe grading of oral involvement and in seven patients, other mucosae were involved. Among 19 patients with moderate skin involvement, 8 were having oral mucosa with grade 2 or 3. Other mucosal involvement was found in seven cases. Out of 4 cases with mild extent of the disease, one patient showed involvement of mucosa other than oral mucosa. According to Hicham T et al, 51.6 % presented with severe pemphigus. Involvement of other mucosa was more frequent in patients with severe disease. No patient with mild pemphigus had lesions in multiple mucosal sites not conforming to the present study. Also they could correlate the number of relapses with pemphigus severity score.⁸ And lower mortality rate was found among pemphigus patients with moderate severity compared to those with severe disease in an American study (Carson PJ et al).⁹

Oral lesions were present in 85.3 % patients, genital lesions in 22.3 %, nasal lesions in 14.9 % and eye lesions in 7.5 % in the present study. In a study done in Turkey, oropharyngeal mucosa was involved in 54.1 % of pemphigus, 8.1 % patients had nasal erosions and similar to the present study, conjunctival mucosa in 7.7 % patients (Yayli S et al).¹⁰ Out of 15 cases with severe (grade 3) oral mucosal involvement, 8 (14.8 %) were females and 5 had involvement of other mucosa. Extent of the body surface area was moderate to severe in 8 (14.8 %) cases. Svecova D observed that independent of the severity of disease, mucosal lesions originated in the oral cavity in 34 (77.3 %) patients. Females were found to have more severe disease in the oral cavity (59.3 %) and in the other mucosa (60.4 %) compared to males. A high oral ABSIS score was seen only in patients with severe pemphigus (27.3 %) and severe mucocutaneous pemphigus was significantly associated with other mucosal involvement.¹¹

In the present study, nail changes were found in 33.3 % patients. Changes like paronychia and dystrophy were reported in 37 out of 141 pemphigus patients by Baghdad B

et al.¹² In 36 patients where Tzanck smear was done, acantholytic cells were found in 55.6 %. According to Kudligi C et al, Tzanck smear revealed acantholytic cells in 28 (90.3 %) cases of PV and all cases of PF and PE.⁷ The major histopathology examination findings were suprabasal cleft in 82.1 % and subcorneal blister in 5.7 % patients in the present study. Out of 36 cases, 65 % showed intercellular IgG and 50 % showed C3 indirect immunofluorescence test. In the study by Chowdhury J et al, out of 41 cases, 87.8 % patients showed acantholytic cells on histopathological examination. Suprabasal blister was found in 62.5 % patients followed by intraspinous in 15.62 % and subcorneal blister in 15.62 % patients. IgG and C3 were deposited throughout the epidermis in majority of pemphigus patients (87.5 %).¹³

Pus culture and sensitivity reports showed 13 % each with Staphylococci and MRSA and in 1.9 % showed Streptococci. An important finding was that two patients died among 15 cases where C & S was positive. Huda et al isolated staphylococcus aureus in 74 % patients.⁶ Majority (94.4 %) of the patients were pemphigus vulgaris and pemphigus foliaceus in 5.6 % in the present study. And in the 20 year study done in Iran, pemphigus vulgaris was the most common clinical subtype (91.15 %) followed by pemphigus foliaceus in 6.4 % and pemphigus vegetans in 2.3 %.¹⁴ In the present study, steroids alone were given in 63 % and for 37 % of patients, other immunosuppressants like Azathioprine, Cyclophosphamide or Methotrexate was given. Out of 108 patients, only 28.7 % received corticosteroids alone in a study conducted in Romania (Baican A et al). Majority of the cases were given corticosteroids along with Azathioprine, Cyclophosphamide, Methotrexate or intravenous immunoglobulins.¹⁵

Associated diseases found in the present study include diabetes in 25.9 %, thyroid disease in 11.1 %, hypertension in 5.6 % and candidiasis in 22.2 %. Ibrahim MA et al have documented oral candidiasis in 48 % patients of 100 pemphigus patients.¹⁶ In the study done in Chicago among pemphigus vulgaris patients, significant association was observed with diabetes mellitus, hypertension and osteoporosis (Hsu DY et al).¹⁷ In the present study, among 54 pemphigus cases, 3 patients (5.6 %) died. Similar mortality rate (5.3 %) was found during the 12 months of follow-up by Mohamad AF et al.¹⁸ In another study done in UK, higher number of deaths (26 %) occurred among pemphigus patients (Langan SM et al).¹⁹

Among the three patients died, 2 were below 60 years and all were females. Out of 3 patients who died, 2 had less than 6 months duration of the disease and one with more than 1 yr. In two of them, Nikolsky's sign was positive and one had severe extensive disease extent. Among the deaths, two had mucosal onset and one with onset of the lesions on skin. In many studies, most of the deaths were observed among patients with onset of pemphigus in older age group ,above 60 years.^{20,21} Similar to the present study, majority of the deaths occurred in females (11 / 17) in the study done in Romania.¹⁵ According to Huang Y H et al, most of the deaths were among males (54 / 88).He also reported 51.1 % deaths in pemphigus patients within first year after diagnosis.²¹ More than 90 % body surface involvement was

present in 50 % cases of whom died from the disease (Nair PS).²² Abdolsamadi HR et al documented that mortality rate was lower in patients with mucous membrane involvement compared to those with skin lesions. This may be due to early diagnosis of the disease and lesser complications due to lower dose of drugs.¹⁴ In the present study, two patients were diabetic and one showed candidiasis among the 3 patients who died. MRSA was isolated in 2 and one had severe thrombocytopenia. One patient was in steroid treated group and the other two were given other immunosuppressants like cyclophosphamide, azathioprine or methotrexate. Hypertension and diabetes mellitus were not found to be related to overall mortality in pemphigus patients in the study by Baican A et al.¹⁵ In the study done in Israel, infections were the most common cause of death (39.6 %) especially pneumonia, skin infections and septicaemia (Kridin K et al).²⁰ In the study by Nair PS, staphylococcus aureus was the commonest pathogen grown and MRSA was isolated in 3 cases who died. Majority of the patients who expired (94.4 %) were on systemic steroids and 5 were on DCP therapy.²²

CONCLUSIONS

Pemphigus patients were of slightly older age group (51-70 years) in the present study. Family history of autoimmune conditions like diabetes was present in 31.5 %, thyroid disorders in 3.7 %, vesiculobullous diseases in 5.5% and vitiligo in 1.8% cases. Diabetes was present in 25.9% and thyroid diseases in 11.1 % of patients. All the 3 patients died were females. Infection could be an important cause of death in these patients but no statistically significant association was found, probably due to the smaller sample size. Another limitation of this study was its retrospective nature.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

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