PEMPHIGUS: A STUDY OF 35 CASES IN KUWAIT AND REVIEW OF THE LITERATURE.

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SUMMARY

In the present report, 35 patients suffering from pemphigus who attended the Dermatology Department at Al-Sabah Hospital in Kuwait for a period varying from 3 months to 10 years between 1981 and 1990 were reviewed. The data concerning age, sex, nationality, type of pemphigus, the duration of the disease, the diagnostic aids, and the result of treatment followed in this group of patients are summarized and discussed.

INTRODUCTION

Pemphigus is a potentially fatal bullous skin disease whose incidence is estimated to be 0.3 - 3.2 per 100,000 per year[1]. Its prognosis has markedly improved as a result of early effective therapy[2] with a drop in its mortality from 60-90% 3 to 5-15%[4].

Pemphigus is an autoimmune intra-epidermal blistering disease and is diagnosed according to its clinical picture with Tzank smear together with histological and immunological tests[5]. The disease has been classified into clinical variants including pemphigus vulgaris (P.V.), pemphigus vegetans pemphigus erythematosus (P.E.) (Senear Usher), pemphigus foliaceus (P.F.) known in Brazil as Fogo Selvagum, and pemphigus herpetiformis[6].

The stimulus that leads to the production of autoantibodies in pemphigus is not known at present. The antibodies (IgG) bind to a pemphigus antigen on the surface of the epidermal cell membrane. This combination may either lead to compliment activation, breaking of the intercellular substance resulting into acantholysis, or it may suppress plasminogen activator inhibitors leading to synthesis of plasminogen activator which acts on plasminogen to produce plasmin that breaks the intercellular substance leading to acantholysis[1].

In P.E., IgG and C3 are deposited in the intercellular spaces and the dermoepidermal junction, an immunopathologic feature of both pemphigus and lupus erythematosus. Circulating antinuclear antibodies are found in 30 - 80% of such cases. P.E. is considered as a localized form of P.F.[7].

Pemphigus herpetiformis is one of the less common forms of pemphigus. Direct immunofluorescence done in 15 cases of pemphigus herpetiformis showed that IgG was detected in the ICS of epidermis in 100% of cases, C3 was found in 83% and IgA in 6.7%. Indirect immunofluorescence was positive in 33.3%.6 During the course of treatment it may change to other forms of pemphigus.

There are data which indicate that activated mononuclear cells are present in lesional skin of pemphigus patients and may contribute to the pathology of this disease[8].

Clinically, pemphigus may or may not itch. The disease is usually characterized by blisters affecting skin and mucous membranes. The bullae are usually flaccid and spread peripherally if slight vertical pressure is applied[9]. The bullae readily rupture with mild trauma leaving moist eroded areas that soon become infected and crusted. Mucous membrane lesions also rupture leaving denuded painful areas.

The most commonly affected sites include the scalp, face, axillae and oral cavity, and this may be because the largest amount of pemphigus vulgaris antigen in normal skin is present in these sites, while the smallest amounts are in the lower back. These findings may suggest that the clinical distribution of lesions may be influenced by regional variation of pemphigus vulgaris antigen[10,11].

It has been estimated that 50-70% of pemphigus vulgaris patients get oral cavity lesions first[12]. The skin lesions follow mucous membrane affection after the elapse of 5 months[4] or even 13 years[13]. Ninety percent will show oral lesions during the course of the disease and some may never develop skin lesions. Mucous membranes other than the mouth may also be affected[5]. Oral lesions are uncommon in P.F. and P.E.[1].

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PATIENTS AND METHODS

Thirty five patients were followed up in the department of dermatology, Al-Sabah Hospital, Kuwait between 1981 and 1990. Data were tabulated according to the age, sex, nationality, clinical description, types of pemphigus, the result of treatment and their monitoring. Pemphigus was diagnosed according to the clinical presentation, Tzank smear, histopathology, and direct and indirect immunofluorescence tests. Other investigations included complete blood count, blood biochemistry, serology, immunology, urine, stool, and x-ray chest.

Patients with wide-spread disease were hospitalized till improvement and later followed up as outpatients once weekly in a clinic run by a consultant and two registrars, and assisted by medical, surgical and laboratory facilities whenever required.

The standard therapy followed was a combinations of prednisolone and azathioprine. The treatment was individualized to some patients as judged by their general condition, associated diseases, the degree of response to a particular drug, laboratory results, and complication that might arise.

The effect of treatment was checked by doing blood count weekly, liver and kidney function every 2 week, and indirect immunofluorescence 3 times for each patient on the average. The indirect immunofluorescence was done on Guinea-pig lip corner mucosa.

RESULTS

The patients' characteristics are shown in Tables 1, 2 & 3. Kuwaitis represented 40% of the group; other Arabs 40% and other nationalities 20%. The overall female to male ratio is 1.9:1. This ratio among Kuwaitis is 2.5:1. The age of onset ranged between 14 to 70 years with a mean of 36.8 years among females and 40.4 among males (Table 4). In this group of patients, the types of pemphigus were in the following order of frequency: Pemphigus vulgaris 74.2%, pemphigus foliaceous 14.3%, pemphigus erythematosus 11.4%. No pemphigus vegetans cases were observed. Table 5 demonstrates the duration of pemphigus.

From patient's history, forty percent reported oral lesions to be the first presenting sign alone and this was exclusively in pemphigus vulgaris, whereas skin and oral mucous membrane were simultaneously involved in 25.7% Oral mucosa was first affected in 65.7% of this group. Skin lesions alone were the first to appear in 34.3% of cases.

None of the patients with pemphigus foliaceous gave history that the mucous membranes were the first to be affected, while one of the four cases of pemphigus erythematosus had oral lesions in the beginning. The overall mucous membrane affection

Table 1. Pemphigus patients according to nationality and sex.

Nationality	Female	Male	Total
Kuwaiti	10	4	14
Other Arabs	9	5	14
Non Arabs	4	3	7
Total	23	12	35

Overall ratio of females to males= 1.9:1. Female to male ratio among Kuwaities = 2.5:1

Table 2. Nationalities of other Arabs according to sex.

Nationality	Female	Male	Total
Jordanian	1	3	4
Iraqi	3	1	4
Syrian	2	-	2
Egyptian	1	-	1
Saudi	2	-	2
Yemen	-	1	1
Total	9	5	14

Table 3. Nationalities of non Arabs according to sex.

Nationality	Female	Male	Total
Indian	3	1	4
Pakistani	-	1	1
Sri Lankan	1	-	1
Thai	-	1	1
Total	4	3	7

Table 4. Age range.

Sex	Age range	Mean
Female	14-65	36.8
Males	24-70	40.4

in P.V. was 84.4% (Table 6).

At the time of examination of patients, the oral lesions alone were present in 14.3% of the patients (exclusively pemphigus vulgaris), skin lesions alone were found in 25.7%, skin and oral mucous membrane in 60% of patients. The oral mucous membrane was affected in 74.3% of all the patients at time of examination (Table 7). Other findings are listed in Table 8.

Pemphigus diagnosis was confirmed by Tzank smear and biopsy in thirteen, Tzank smear alone in 6, biopsy alone in 6, direct immunofluorescence and indirect I.F. in 14 patients. Circulating immune complexes were estimated for eleven patients and only 3 were positive (2 P.E. and one P.F.) (Table 9).

During the follow up period that ranged from 3 months to 10 years, indirect immunofluorescence was repeatedly done (Table 10). The relation of this test to the activity of the disease is shown in Table 11. Two blood samples taken from patients who were free from skin and mucous membrane lesions had a titer of 1:40, and 15 samples taken during mild clinical disease under treatment were negative in the titer of 1:20. Other routine laboratory investigations showed in 12% of patients blood eosinophilia ranging from 6-12% with a mean of 12% per c.mm.

Evaluation of treatment (Table 12)

Twenty five patients were treated with combined prednisolone and Imuran. The daily dose of prednisolone ranged from 40-200 mg and Imuran 100-200 mg. Remission occurred within 1-8 weeks with an average of 4 weeks. Thereafter prednisolone was gradually reduced to 15-30 mg on alternate days and Imuran to 50-100 mg daily. Out of twenty five patients, four patients 11.4% (3 males with pemphigus vulgaris and one female with pemphigus erythematosus) were in remission. Three of these four patients stopped treatment for 4 years and one for 6 months. Twelve patients of this group were controlled and had minimal lesions and were maintained on 15-30 mg prednisolone on alternate days and 50-100 mg Imuran daily. Six patients improved but failed to come for follow up. Three patients died while on this combined treatment (Table 13).

Nine patients were treated with prednisolone alone 40-120 mg daily because Imuran was contraindicated. Remission occurred within 2 to 5 weeks. Two of the nine patients were maintained on 30-45 mg of prednisolone and 7 on 15 mg on alternate days. Four of the nine were followed up for 4-7 years and five for 12-16 weeks. A tenth patient with pemphigus vulgaris did not respond to high

Table 5. Types of pemphigus related to sex and duration of disease.

	DURATION IN YEARS												
Type of Pemphigus	0 - 1		1 - 2		2 - 5		6 - 10		> 10		Total		%
	M	F	M	F	M	F	M	F	M	F	M	F	
Pemphigus Vulgaris	4	1	-	2	2	8	6	2	-	1	12	14	74.3
Pemphigus Foliaceous	-	-	-	1	-	3	-	-	-	1	-	5	14.3
Pemphigus Erythem.	-	2	-	-	-	1	-	1	-	-	-	4	11.4
Total	4	3	-	3	2	12	6	3	-	2	12	23	100
Duration in term of percentage	20		8.6		40		25.7		5.7				

M = Male. F = Female

Table 6. Sites of onset of lesions as reported by the 35 patients.

First lesion at onset	P. V.		P. F.		P. E.		%
	M	F	M	F	M	F	
Mucous membrane alone	8	6	-	-	-	-	40
Skin alone	2	2	-	5	-	3	34.3
Skin+ M.M.	3	5	-	-	-	1	25.7
Total	13	13	-	5	-	4	100

P.V.= Pemphigus vulgaris. P.F.= Pemphigus foliaceous. P.E.= Pemphigus erythematosus.

Table 7. Lesional distribution at time of clinical examination.

Lesions found at examination	P. V.		P. F.		P. E.		%
	M	F	M	F	M	F	
Mucous membrane of mouth	1	4	-	-	-	-	14.3
Skin alone	2	-	-	4	-	3	25.7
Skin+ M.M. 10	9	-	1	-	1	60	
Total	13	13	-	5	-	4	100

P.V.= Pemphigus vulgaris. P.F.= Pemphigus foliaceous. P.E.= Pemphigus erythematosus.

doses of prednisolone (120 mg) and responded when dapsone was added.

Steroid side effects were Cushingoid features, diabetes, steroid acne, striae, pyoderma, heart burn, and hypertension.

DISCUSSION

In the present work, the diagnosis of pemphigus was confirmed by laboratory diagnostic aids (Table 9). The history taken from the patients showed that the onset of the lesions was in the mouth in 40%, skin in 34.3%, and both skin and mucous membranes in 25.7% with an overall mucous membrane affection of 65.7% (Table 6). Out of the 26 patients with pemphigus vulgaris, 14 (53.8%) showed oral cavity lesions as the first to appear.

The overall mucous membrane affection of the mouth in the course of PV in this series was 22 patients i.e. 84.6% (Table 6). At the time of clinical examination, 60% of the patients had skin and mouth lesions, 14.3% had mouth lesions alone and all were PV and 25.7% had skin lesion alone (5.7%, P.V., 11.5% P.F. and 8.5% P.E.) (Table 7).

Twenty five percent of patients with P.E. and 20% of patients with P.F. developed mouth lesions in the course of the disease, while none of them had such lesions at onset of disease. The site of initial lesions may influence prognosis of the disease[2].

Cases where the skin is the only site affected have the highest percentage of clinical remission and lowest percentage of exacerbation. Involvement of oral mucosa may reflect a worse prognosis[2].

All our patients complained of itching especially when new lesions are erupting. None of them gave

Table 8. Other findings.

1.	No history of exposure to chemicals, toxins or drugs
2.	Main sites affected were trunk, scalp, ambilicus, mucous membrane of the mouth, extremities, chest and back.
3.	The lesions in pemphigus vulgaris were either vesiculobullous or crusted.
4.	The scalp was affected in 14 out of 35 cases
5.	All patients complained of itching especially when lesions were erupting
6.	No associated systemic condition was detected.

history of exposure to chemicals. Krain[4] reported that 29% of his series were exposed to chemicals such as chlorine gas, mercury dichloride, and industrial solvents.

None of our patients gave history of exposure to drugs. There are reports about pemphigus induced by drugs such as penicillamine[14,15], rifampicin[16], phenobarbital[17], penicillin[18], and captopril[19].

It is assumed that penicillamine possibly alters the intercellular substance (ICS) into antigenic structure possibly by the action of sulfhydryl group. Penicillamine-induced pemphigus occurs in 3 to 10% of cases treated with penicillamine. The penicillamine-induced pemphigus commonly has the features of P.F. rather than P.V., and usually clears when the drug is discontinued but 30% may need systemic steroid and/or Immune suppression.

In the present series there were no associated diseases. Pemphigus associated with myasthenia graves, thyroid disease, and malignant disease has been reported[13,20,21].

The female to male ratio among Kuwaiti patients (Table 1) was 2.5:1, and the youngest patient affected was 14 years old (Table 4) compared to 3.5 years in other reports[22].

The types of pemphigus seen in this series, their duration, their frequencies, their clinical pattern, the diagnostic aids used, the indirect immunofluorescence results in relation to the clinical presentation, and follow up of pemphigus activity are all shows in Tables 5,6,7,8,9,10 and 11. Other routine tests were done regularly to monitor the effect of treatment. The blood count showed eosinophilia in 12% of patients compared to 10 - 45% reported in a group of patients[23].

The pemphigus duration in this series was less than 2 years in 28.6 of patients, between 2 and 10 years in 65.7% and above 10 years in 5.7% (Table 5). Prognosis for survival was better when disease duration was prolonged beyond 4 years, and most deaths occur with disease duration of less than one year[2].

The results of indirect immunofluorescence and its relation to disease severity are shown in Tables 10 & 11. None of the patients had a titter over 1:320. Two patients showed a titer of 1:40 while they had no skin lesions. In a review of 1500 cases, 1% had pemphigus antibodies without pemphigus[24,25]. In this series, 15 patients with skin lesions had negative results in 1:20 dilution. The failure of antibody titers to reflect clinical disease has been noted. Fitzpatrick and Newcomer[24] found, in general, that there is a significant correlation between titer and disease activity, but they found also that serial titers are not reliable as a therapeutic guide or a prognostic indicator in pemphigus. A low titer may not correlate with low disease activity and may not necessarily imply a good prognosis. Negative titer may not mean prolonged remission. Conversely, a high

Table 9. Diagnostic aids.

Test	No. of patients	Results
Tzank Smear	19	19 Positive
Biopsy	19	Confirmed diagnosis
Tzank smear + biopsy	13	+ve for acantholysis and histopathology confirmed
Direct I.F.	14	+ve 14
Indirect I.F.	14	+ve 14
C.I.C.	11	Raised only in 3 (2 P.E., 1 P.F.)

I.F.= Immunifluorescence. C.I.C.= Circulating Immune Complexes.

Table 10. Indirect immunofluorescence tests in different dilutions.

Number of patients 34					
Dilution of test	1 : 20	1 : 40	1 : 80	1 : 160	1: 320
Number of tests done	98	55	19	2	1
Number of positive tests	55	19	2	1	1
Number of negative tests	43	36	17	1	-

Table 11. The indirect immunofluorescence results in relation to severity in pemphigus.

Dilutions	1:20			1:40			1:80			1:160			1:320		
Results	Neg	+	++	Neg	+	++	Neg	+	++	Neg	+	++	Neg	+	++
Severe			6		4	2	4	2		1	1		1		
Moderate		11	5	9	7		7								
Very mild	15	12	5	13	4		4								
Free	28	12	4	14	2		2								

Severe = Many lesions (more than 10) scattered all over the body.

Moderate = Few blisters (4-10 lesions) scattered in 3 sites of the body.

Very mild = 2-3 lesions usually in one place.

Free = No blister on skin or mucous membrane.

titer did not imply severe disease or a worse prognosis[24].Others believe that monitoring of pemphigus antibody is a valuable tool to regulate therapy and prevent prolonged administration of toxic drugs when they may no longer be indicated[25].

Comparison of the results in the present work to six similar published data[2,4,12,13,26,27] is shown Table 14. Similar findings regarding female to make ratio, age incidence, types of pemphigus, and mortality with some differences especially the absence of pemphigus vegetans were noted in Kuwait series.

There have been many reports discussing treatment of pemphigus and its outcome. Lever et al.[27,28,29] gave the following guide lines for treatment of pemphigus:

1. High dose Prednisolone was recommended for patients with extensive lesions. The dose varied from 180-300 mg per day according to disease severity. The high dose is given for 6-10 weeks after clearance of all lesions then the dose is reduced to 40 mg daily. Thereafter, alternate-day dosage is advised. The reduction should be more gradual to reach zero level in about 16 months (Table 15). If exacerbation occurs, 120 mg at least should be given daily for several weeks.

This line of treatment is well tolerated but serious side effects may occur with subsequent treatments. Results of high dose prednisolone treatment in three groups of patients were published by Lever et al.[12]. These results are summarized in Table 16 that shows a group of 12 patient who were treated with high dose prednisolone had a total mortality of 41.3%. Fifteen other patients were initially treated with high doses and subsequently given Methotrexate and maintenance Prednisolone with a total mortality of 20%. A third group of 10 patients was treated with high doses of Prednisolone and when controlled, they were maintained on alternate Prednisolone plus daily immunosuppressors with a total mortality of 20%.

2. Combined Treatment[28,29]: Patients in early stage were given initial dose of 40 mg Prednisolone

Table 12. Evaluation of treatment in the present study.

						Deceased		
Treatment given	No of patients cured & stopped treatment	Follow up period	Number improved with minimal lessions and maintained on treatment	follow up period	Number improved but no follow up	Cause related to	Unrelated cause	Total
Combined Prednis. and Imuran	4	3 Patients for 4 years patient for 6 months	12	1-10 years	6	1	2	25
Prednis.	-	-	4	4-7 years	-	-	-	9
			5	3-4 month				
Prednis. and Dapsone	-	-	-	-	1	-	-	1
Total	4	-	21	-	7	1	2	35

Prednis. = Prednisolone.

on alternate days plus immunosuppression. The immunosuppressive drugs used were either Methotrexate 20 mg once a week, or Cyclosphosphamide 100 mg per day or Azathioprine 150 mg per day. When patients clear in several months to a year or more, Prednisolone dose is reduced 5 mg every month till a dose of 15 mg. Thereafter, 5 mg are reduced every 2 month. It takes 10-12 months to reach zero level of prednisolone. The immunosuppressants are reduced to zero in 6 months. If recurrence occurs the dose of Prednisolone is increased.

This regimen saves the side effects of high doses of Prednisolone. A group of 16 patients was put on this combined treatment. Three patients (18.7%) had a flare up and needed high doses of prednisolone, 13 were well controlled. Follow up of these 16 patients was for 3 months to 4 years. Five had few lesions and were under treatment, 6 had no lesions and were under treatment, 5 were free and were on no treatment. No mortality was reported in this group.

3. Immunosuppressants alone[28,29]: A group of 10 patients only were treated. Nine used Methotrexate and one was treated with Cyclophosphamide. Four cleared but one of them had recurrence and was controlled by immunosuppression alone. Five got acute exacerbation and high dose Prednisolone had to be given, and one died (mortality 10%).

Immunosuppressants and high dose Prednisolone was recommended for treatment of severe pemphigus vulgaris. Such combinations included azathioprine 100-200 mg per day combined with Prednisolone 150-200 mg daily[30,31]. This combi-

Table 13. Deceased pemphigus patients in the present study.

Age	Sex	Nation.	Diagnos.	Duration	Treatment	Cause of Death
26	M	Kuwaiti	Pemph. vulgaris	3 months	High dose Prednisolon & Imuran for 3 months	Pulmonary infection
24	F	Kuwaiti	Pemph foliaceous	11 months.	Prednisolon + Imuran for 11 months	Heart disease
43	M	Jordanian	Pemph vulgaris	6 years	Prednisolon + Imuran for 6 years	Heart attack

nation is safe and effective with a mortality of 7%. Cyclophosphamide was given in the dose of 100-200 mg daily with Prednisolone 200 mg per day[32]. Methotrexate and high dose Prednisolone was also given[33] and is effective and has a mortality rate of 8%.

Other lines of treatment include: Gold therapy; large doses of Prednisolone folowd by gold was given for 15 patients. Gold alone was given for 3 patients. Eight patients got remission that did not need treatment. Gold is useful especially in patients who do not tolerate immunosuppression[34,35]. Plasma exchange and plasmapheresis are rational treatment to manage severe pemphigus and are not practical for routine management[36,37,38]. Plasmapheresis in conjunction with high doses of steroids and immunosuppressive drugs reduces circulating levels of pemphigus antibodies more rapidly than conventional therapy[39]. Extracorporeal photopheresis[40], Dapsone[41], and cyclosporine[42] are other treatment modalities of pemphigus.

In the present series, 25 patients were treated with a combination of prednisolone and imuran, 9 patients with prednisolone alone, and one with prednisolone plus dapsone. Best results were obtained with combination of Prednisolone and Imuran. Ten patients could not be given immunosuppressants because of contraindications and so had to be managed on steroids alone. One of these ten patients did not respond to high doses of prednisolone and had marked side effects (Cuahingoid features, hypertension and diabetes). This patient responded well to combination of prednisolone and dapsone 100 mgm daily dose. Four among the 25 patients who received combination of prednisolone and imuran had complete clearance and were in remission during follow up period (3 patients for 4 years and one patient for 6 months). The rest of the patients were maintained on prednisolone (dose ranging from 5 to 40 mg on alternate days). We observed a mortailty rate of 8.6% (3 out of 35 patients) (Table 13).

Lever[29] found in a series of 67 patients seen between 1961-75 that 10% died from complications of treatment, 8% died from causes not related to disease or treatment and 40% went into remission with no need for treatment. Fifteen percent required low dose maintenance with glucocorticoid and or immunosuppressive drugs in order to remain in remission, and 27% had moderately active disease with continued relapses and remissions.

In conclusion, the course of pemphigus is variable and unpredictable for a given patient. Pemphigus remains a disease that will not yield to "a cook book" approach and whatever the guidelines are, an individualized approach must remain the goal[13].

Acknowledgement:

My deep thanks are due to Mrs. Winnifred Gonsalves, the secretary of the Department of Dermatology & Venereology at Hamad Medical Colrporation, Doha, Qatar; as she did her best to type this paper.

Table 14. Comparative studies

References Number	2	4	12	13	26	27	Kuwait series
Total patients reviewed	115	59	70	107	89	46	35
Female : Male	1.5:1	1:1	1:1.3	1:1	-	-	2.5:1
Pemphigus Vulgaris	88 76.5%	49 83.1%	41 58.%	85 79.5%	71 80%	32 69.6%	26 74.3&
Pemphigus Vegetans	7 6.1%	1 1.7%		5 4.7%	4 4.4%	1 2.1%	
Pemphigus Foliaceous	3 2.6%	8 13.5%	8 15.7%	6 5>7%	5 5.6%	11 23.9%	5 14.3%
Pemphigus Erythem.	17 14.8%	1 1.7%	21 25.8%	11 10.1%	5 5.6%	2 4.4%	4 11.4%
Type not shown					4 4.4%		
Age	40-60	(12-79) 64.5		14-88			14-70
Living Patients	90 78.3%	41 69.5%	36	64 59.8%		30 75%	20 57.2%
Dead	25 21.7%	13 22.1%	30	43 40.2%		16 26%	3 8.6%
Unknown		5 8.4%		1st 10 yrs. 46% 2nd 10 yrs. 24%			12 34.2%

Table 15. High dose prednisolone course therapy[27]

Dose(mg)	Duration of recommended dose
180-300	Continued for 6-10 weeks after clearance of leasions
40	For one week
30	For one week
25	For one week
40	On alternate days
Reduce 5 mg every 2 months to reach zero (in about 16 months)	

Table 16. Results of high dose prednisolone treatment in three groups of pemphigus patients[27]

		RESULTS				
Group	No. of patients	NO lesions + No Treatment	No Lesions+ Maint-enance	Few Lesions +Maint-enance	Died from side effects	Died from unrelated cause
1	12	6	-	1	3	2
2	15	4	1	7	-	3
3	10	4	2	2	2	-

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