Indian Journal of
Dermatology & Venereology
(Incorporating Indian Journal of Venereal Diseases & Dermatology)

Vol. 36; No. 1. January-February 1970

CLINICAL ARTICLES

A STUDY OF 100 CASES OF PEMPHIGUS-CLINICAL FEATURES

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Introduction Pemphigus is not an uncommon disease. But in the last 15 years only a few papers on this subject have appeared in the Indian literature[1,13,18]. A study of 34 patients reported by Kandhari and Pasricha[13] is the largest series so far. Varied clinical facets of pemphigus have been observed in various clinical types of the disease. The prognosis of pemphigus varies still from type to type and in the same type from subject to subject. Pemphigus vulgaris still carries the worst prognosis in spite of steroids. Pemphigus foliaceus is less severe, but still a formidable disease.

It was previously brought out by one of us (SCD) that pemphigus seborrhoecus arises denovo or as a stabilised phase of pemphigus foliaceus[9]. Apart from occasional generalised flare-ups, which could be controlled by steroids, it had the best prognosis. Here we present our further experiences on the subject. We prefer to use the term pemphigus seborrhoecus, because it was the first correct description of the disease syndrome made by Touraine and Lortat-Jacob[24]. This had been referred to as pemphigus erythematosus by American workers, this name having been introduced by Senear and Usher. However, Senear himself advocated dropping of this term[9]. Recent immunopathological findings[4] in Senear Usher syndrome suggesting a co-existence of pemphigus with lupus erythematosus raises the issue of the possibility of a separate entity unlike pemphigus seborrhoecus which we have found on prolonged clinical observations (Senear-Usher Syndrome) to be a stabilised phase of pemphigus foliaceous.

In this paper we present some interesting clinical and histopathological data on 100 cases of the different types of pemphigus recorded in the pemphigus registry of our deparment from 1955 to 1968. We will bring out our further

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Received for publication on 24-9-69.

observations on the two types of acantholytic cells found in pemphigus and reported before[9]. Our experiences on treatment will be reported in a subsequent paper.

Material and Methods. This study on 100 patients included some of those from the previous report[9]. Out of 100 patients 69 were of pemphigus vulgaris, 18 of pemphigus foliaceus and 13 of pemphigus seborrhoecus.

Detailed history and clinical findings were recorded. Routine investigations such as complete blood counts, urine and stool examinations, blood proteins, blood grouping and cross-matching and biopsies of fresh and intact lesions were carried out.

Corticosteroids were prescribed together with appropriate local ancillary measures only after all the investigations were done. The patients were regularly examined and special emphasis was laid on the appearance of new lesions, the way in which the old lesions healed and the changes in their morphological features, suggesting transformation from one type of pemphigus to another. A watch was kept for the side effects of steroids.

When the lesions cleared up or the disease had stabilised on fairly low dosage of corticosteroids, the patients were asked to report as out-patients every fortnight for regular assessment. In case there was deterioration of the condition the corticosteroids dosage was stepped up.

Age and Sex Incidence. This is given in Table No. 1. The majority of our 100 patients were in the age groups of 22 to 60 years (89%) and there was no significant difference in the age incidence in the different clinical types of pemphigus. Forty-nine patients were between 22 and 40 years of age, which was lower than that reported by the western authors who claimed the maximum incidence to be between 40 to 60 years and above[3, 6, 7, 10, 15, 17, 19, 21, 22]. The youngest patient was of pemphigus foliaceus at the age of 16 years. Perry[17] has recorded a similar case at the age of 11 years. There were only five patients above the age of 60 years in our series (5%), while in Costello's series 80% of the patients were more than 60 years of age[7].

Table No. 1

Age and sex Incidence of Pemphigus

Type of Pemphigus & No. of Pts.		.....AGE..... 15-21	22-40	41-60	>60	Males	Females
Pemphigus Vulgaris	69	5	32	27	5	37	32
Pemphigus Foliaceus	18	1	10	7	—	10	8
Pemphigus Seborrhoecus	13	—	7	6	—	10	3
Total	100	6	49	40	5	57	43

In a series reported by Kandhari and Pasricha[18] from Northern India 5 patients were less than 20 years old, the youngest being 9 and majority were between 31 to

50 years of age. Similary more than half the number of patients were 20 to 40 years old, and the youngest was 5 years of age in a series reported by Ambady et al[1] from Southern India. This corroborated with the age incidence in our patients and we feel that the disease manifests at a younger age in Indians.

The disease seemed to affect both the sexes equally. We had a slight preponderance of males over females in the vulgaris and seborrhoecus groups which might be explained by the larger number of male patients attending the hospital.

General Symptomatology of Pemphigus

Pemphigus Vulgaris:—We graded out patients of pemphigus vulgaris into severe or malignant and moderate varieties depending on the extent of the disease, its evolution and associated toxaemia. The severe variety was characterised by rapid spread of the disease within 3 months of onset, with wide spread skin involvement and marked toxaemia characterised by fever and a high pulse rate. The moderate variety was characterised by slow evolution of over 6 months or more, lesser involvement of the body surface and little or no toxaemia and fever. Grading in this fashion brought out clearly the differences between different types of pemphigus, as very few cases of foliaceus and none of seborrhoecus had the severe disease. Additionally, it also helped in judging the prognosis and the assessment of treatment.

Twenty-eight out of 69 patients had malignant pemphigus vulgaris. These included 7 patients who had fulminating relapse due to the sudden stoppage of corticosteroid therapy. The remaining 41 patients were of moderate severity (Table No. 2).

Table No. 2.

Symptomatology of Pemphigus

Type of Pemphigus		Pemphigus Vulgaris	Pemphigus Foliaceus	Pemphigus Seborrhoecus
Total Number of Patients		69	18	13
Course	Severe	28	2	—
	Moderate	41	16	13
Fever		22	7	—
Itching		8	8	8
Burning		54	12	7

Fever was present in 22 of the 28 patients with severe disease.

While itching occurred in only 8 of our patients (13%), 54 complained of burning (80%). Similar features in the symptomatology of pemphigus vulgaris had been recorded by others[7,10,15,22].

Pemphigus foliaceus

As a rule, pemphigus foliaceus had a milder course than pemphigus vulgaris. In 16 patients, the disease was moderate, in 5 of whom there was low lever but the general condition of all the patients was good. In 2 patients it was severe with toxaemia, high fever and more generalised eruption.

Both itching and burning sensations in the lesions were seen in this disease. Itching was the symptom in 8 and burning in 12 patients. Burning was not as severe as that experienced by the patients of pemphigus vulgaris. This contrasted with Perry's[17] experience of burning and or itching in 90% of patients with pemphigus foliaceus.

Pemphigus seborrhoecus

Pemphigus seborrhoecus had the mildest course which was chronic and without fever or toxaemia. Burning was observed in 7 patients and disturbing itching occurred in eight.

Thus fever, toxaemia and generalization of the disease indicated a severe disease process in all types of pemphigus.

Distribution of Lesions in Pemphigus In figure No. I we have compared the distribution of lesions in the three types of pemphigus, and it has helped to distinguish the types. In pemphigus vulgaris, lesions occurred anywhere on the skin. The scalp was involved in 36 (53%) patients; while only an occasional patent had transient lesions on the face. These lesions resembled those of pemphigus seborrhoecus. However, the disease revealed itself by more constant oral involvement and generalization of bullous eruption at some time in its course.

Lesions occurred on the palms and soles in 12 patients of pemphigus vulgaris (17%). In 8, they appeared later in the course of the severe disease and 4 of these patients succumted. This gave us an impression that involvement of palms and soles indicated a worsening prognosis.

Scalp together with the butter–fly area of the face were prominenty involved in 15 patients of pemphigus foliaceus and 12 patients of seborrhoecus. In addition, other seborrhoec areas (mid–chest and inter–scapular region) were also involved in many of the patients. Hence we did not agree with the view[22] that the involvement of the butter–fly area is a feature only of pemphigus seborrhoecus. This idea was responsible for many reports of erroneous diagnosis between the two types. In pemphigus foliaceus, in addition to the butter–fly area of the face the disease tended to be generalised and covered the whole body, while polymorphic lesions with kaleidoscopic transformation seen in the seborrhoetcus type were absent (vide infra).

Mucous Membranes:—Mucous membrane involvement was not encountered in our patients of pemphigus foliaceus and seborrhoecus unlike the experiences of Lever,[15] Perry[17] and Coombes and Canizares[6].

This helped us in differentiating these varieties from vulgaris.

The following table shows the nature of mucous membrane involvement in 69 patients of pemphigus vulgaris.

TABLE No. 3.

Mucosal lesions in 69 patients of pemphigus vulgaris

Mucous Membrane	Number of Patients	Incidence
Oral	58	83%
Genital	17	24%
Conjunctival	11	16%
Laryngeal	2	3%

The oral mucosa was involved (in 58 (83%) patients of pemphigus vulgaris) (at one time or the other) and our experience conformed with the western reports[6,10,15,19,21]. Rarely have we encountered intact bullae in the oral cavities. Usually, the patients showed only erosions. Two other features of oral lesions of pemphigus vulgaris were noted viz., (1) oral lesions preceded the skin involvement bys everal months in 20 patients (29%), and (2) the oral involvement persisted after the skin lesions disappeared in 17 patients (23%).

Genital lesions occurred in 17 patients (24%), and conjunctival involvement in 11 (16%), and larynx was involved in two. Our experience corroborates with that of others in this respect.[6,10,15,19,21,22].

Morphological features of lesions of pemphigus:—Morphological features of these lesions are brought out in figures 2, 3, 4 and 5 (photographs).

Bullae in pemphigus vulgaris were tense to start with in some cases, but mostly they were flaccid. In 61 patients they occurred on normal skin while in 8 patients they were surrounded by zones of erythema. In 20 patients there was secondary infection with purulent contents in the bullae. After the bullae ruptured, raw areas were left, which became crusted. Lesions healed without scarring but with hyperpigmentation, which subsequently cleared up. Sometimes non-spreading verruccid, crusted, dark brown lesions replaced the typical vulgaris lesions on adequate steroid control (figure 3b). Such lesions did not disappear for years, and the patients were none the worse for it. Hence we considered this sign as an evidence of stabilization.

Lesions in pemphigus foliaceus were surrounded by zone of erythema in 13 patients. The bullae were flaccid, and adherent in the center with circinate, exudative, crusted edges sometimes giving an appearance of circinate impetigo. On extension, they fused with others to form figurate borders (figure 4b). Such an evolution was observed in about 90% of the patients.

In pemphigus seborrhoecus flaccid bullae of the foliaceus type were seen at some time or the other in the course of the disease in all the patients. In 8 patients there was circum-bullous erythema, but which was not a prominent feature. In all the 13 patients the lesions were greasy, and of petaloid or verrucoid type with adherent crusts, resembling seborrhoea petaloides. (figure No. 5). The lesions were more exudative than those of pemphigus foliaceus. Hence a kaleidoscopic transformation between the variegated lesions was a prominent diagnostic sign of this type. In our opinion, there has been a lack of appreciation of these features of the lesions of pemphigus seborrhoecus.

Nikolsky's sign was positive in all types of pemphigus.

Clinical Transformations In the previous article[9] from our department it was brought out that pemphigus foliaceus and pemphigus seborrhoecus could undergo transformation from one type to the other. Pemphigus seborrhoecus could arise de novo or result as a stabilised state of pemphigus foliaceus with corticosteroid treatment. It could remain localised for many years without corticosteroid therapy (5 years in one of our subjects) or it could deteriorate into generalised pemphigus foliaceus. Our further experience confirmed this view, and in addition, we noted similarity in histopathological changes between the two diseases.

4 patients of pemphigus foliaceus were stabilised to the seborrhoecus type with treatment. Conversely 8 patients of pemphigus seborrhoecus, regressed to the foliaceus state all of whom again reverted to the seborrhoecus type after adequate steroid dosage.

Costello[7], Sanders et al[21], Sanders and Nelson[22], and Rook and Waddington[19] have mentioned about the transformation between pemphigus vulgaris and pemphigus seborrhoecus. Costello[7] reported that pemphigus vulgaris remained localised as pemphigus seborrhoecus for a long time before a typical picture of pemphigus vulgaris developed with extensive skin and mucous membrane involvement, We felt that these differences of view points could be due to a lack of proper appreciation of the clinical features of pemphigus seborrhoecus mentioned above. Hence we had tabulated the differences between the three types of pemphigus before[9]. Lever[16] and Perry[17] have now adopted a similar approach. Lever[16] has further defined this syndrome, and brought out its similarity to pemphigus foliaceus. According to this definition, pemphigus seborrhoecus is localised foliaceus and on deterioration transforms to the foliaceus state only. Reasons for proposing such a rigid definition have been stated by him. Mistakes in judging the type could occur if only the distribution was considered, since erly localised pemphigus vulgaris (which was sometimes observed) on the face could be erroneously considered as pemphigus seborrhoecus. Later occurrence of other features of generalised pemphigus vulgaris gave an impression of pemphigus seborrhoecus transforming into pemphigus vulgaris.

Histopathology Though Auspitz[2] had seen acantholysis in 1881, it was not until 1943, when Civatte[5] recognised the implication of this finding, that interest in this important histopathological feature was aroused. Civatte stressed that the

primary change in pemphigus was intra-epidermal with acantholysis and that it could be utilised to differentiate pemphigus from dermatitis herpetcformis and erythema multiforme. He observed acantholysis in pemphigus vulgaris, vegetans and foliaceus. Subsequently Civatte's findings were confirmed in many reports[3,9,11,12,14,15,16,20], and now it is generally accepted that acantholysis is a prerequisite for the diagnosis of pemphigus. In addition to acantholysis, histological observations have been extended to the levels of the splits and presence or absence of keratinisation of the acantholytic cells for differentiating different types of pemphigus[3,9,10,14,16,17]. Previously it was brought out by one[9] of us that.two types of acantholytic cells could be recognised suggesting different phases of keratinization within these cells. In 1948 Tzank[25] described the test in which stained smears of scrapings from the floors of fresh bullae of pemphigus showed acantholytic cells.

Although acantholysis was observed in all of our 100 patients in the course of the disease, detailed histopathological study could be made on 67 slides only. In the remaining patients where small bullae were not available for biopsy, only Tzank test was performed. Two features were specially looked for viz., (i) the level of the split, and (ii) the type of staining reaction of the acantholytic cells. Our findings are given in Table No. 4 and described in detail below.

TABLE No. 4

Analysis of Histopathological Observations on 67 Sections of Pemphigus

Type of Pemphigus	LEVEL OF THE SPLIT			TYPE OF ACANTHOLYTIC*			
	Total number of specimens	Suprabasal	Sub-corneal tomid- epi-dermal.	Variable Levels *	CELLS Type 'A'	Type 'B'	Dyskera-totic cells
Pemphigus Vulgaris	46	40	—	6	23	23	—
Pemphigus Foliaceus	10	—	8	2	—	10	1
Pemphigus Seborrhoecus	11	4	8	—	3	8	1

* Either the levels of splits varied in the bulla under observation, or splits were observed at different levels in the same section.

* Type 'A' – Fuzzy basophilic cytoplasm with large not-condensed nucleus and perinuclear halo.

Type 'B' – Well defined eosinophilic cytoplasm and condensed pyknotic nucleus.

Pemphigus Vulgaris:—Out of 46 specimens, 40 showed suprabasal splits. The floors of the bullae were formed by basal cells, and occasionally one or two layers of malphigian cells were observed above the basal layer in parts of the sections. The roofs were formed by the rest of the epidermis. Bullous cavities showed variable contents consisting of serous exudate, polymorphonuclear leucocytes, occasional eosinophils and acantholytic cells. In addition to the main bullae, small and ragged areas of suprabasal tears were often seen elsewhere in the same sections (Fig. 6 a).

These early lesions showed oedema of the basal and suprabasal layers, partial acantholytic cells with loss of intercellular bridges and small lacunae. The cells around the hair follicles and sebaceous glands also showed acantholysis in some sections.

In 6 sections the split in the epidermis were observed at more than one level. In some areas, in the same bulla the floor shelved from the subgranular location at one angle to suprabasal location at the opposite angle. (Fig. 6 b). In others one split was located above the midepidermis while another split was seen below this in the suprabasal area giving a picture of a "bulla above a bulla" (Fig. 6 c). Such findings have been reported by Director[10].

In no instance did we find a split or bulla located in subcorneal or midepidermal level exclusively. Even in those 6 sections that showed varying levels of splits, there were suprabasal involvement in the main bullae as well as in the adjacent areas. This study confirmed Lever[16] view that the predominant and early change in pemphigus vulgaris was a suprabasal splits. The varying levels in the split could be explained by regenerative changes accompanied by production of secondary splits.

As reported previously, we again observed two types of acantholytic cells[9]. Type 'A' was a cell having fuzzy basophilic cytoplasm with a large non-condensed nucleus and a perinuclear halo (Fig. 7 a). Type 'B' was a cell with a well defined eosinophilic cytoplasm and a condensed pyknotic nucleus (Fig. 7 b). Both types of cells were seen in the majority of the sections. In 23 specimens, type 'A' cells predominated and in the other 23, type 'B' predominated

We did not encounter dyskeratotic cells resembling grains of Darier's disease.

Pemphigus foliaceus:—In 8 out of 10 sections of pemphigus foliaceus, the splits were located subcorneally or in the upper epidermis only (Fig. 7 b). These findings confirmed those described by Lever[16], Perry[17], Furtago[11], Brennan and Montgomery[3] and Sanders and Nelson[22].

In 2 sections, the levels of the splits were different. In one, the split was subcorneal at one angle of the bulla and suprabasal at the other angle. In the other slide, in addition to a main midepidermal bulla, a small suprabasal vesicle was observed in another area of the same section. However, the absence of type 'A' cells and the presence of only the type 'B' cells, helped in distinguishing this suprabasal split from that of pemphigus vulgaris. This single suprabasal cleft was a rare finding. (Fig. 8 a). Perry[17] has also recorded similar finding. Originally Lever[15] was of the opinion that the suprabasal splits did not occur in pemphigus foliaceus. But in his recent monograph[16] he has mentioned that although rare, such a change was possible in pemphigus foliaceus, and then too in localised area only. He has further elaborated this by stating that when such a split occurs in pemphigus foliaceus, the individual basal cells are not separated from each other in "tomb stone fashion" as observed in pemphigus vulgaris. Contents of the bullae were similar to those of pemphigus vulgaris. In all the 10 sections acantholytic cells of type 'B' were exclusively seen.

In one section we observed hyperkeratosis, follicular plugging and type 'B' acantholytic cells, which were more mature than usual (Fig. 8 b). The keratinization process was still short of fully matured keratin. These findings of variable keratinization of acantholytic cells supported our previous contention that pemphigus should be viewed as a disease of abnormal keratinization and its genesis should be searched for in the studies on the histochemistry of keratin.

Pemphigus Seborrhoecus:—Out of 11 sections of pemphigus seborrhoecus, 8 showed the splits to be either sub-corneal or below the granular layer. In 8 of the 11 biopsy specimens, acantholytic cells of type 'B' were predominantly seen (Fig. 8 c) while type 'A' cells were predominant in the remaining three. One of the sections showed dyskeratotic changes as seen in a case of pemphigus foliaceus.

From our limited but detailed study of 21 sections of pemphigus foliaceus and pemphigus seborrhoecus, we found that these two diseases were histopathologically similar. Both showed more differentiated keratinised acantholytic cells with an occasional dyskeratotic change. Hence we gathered the view that the acantholytic cells of type 'B' indicated a less severe pemphigus process. This feature could be used as an index of prognostication in a particular subject. Our other findings agree with those of Lever[16], Perry[17] and Brennan and Montgomery[8], who considered that pemphigus foliaceus and pemphigus seborrhoecus were histopathologically one and the same disease.

SUMMARY

A clinical study of 100 patients and a detailed histopathological report of 67 slides of pemphigus are reported. Half the number of patients are of the younger age group of 22 to 40 years.

Pemphigus vulgaris presents with two grades of severity. The severe type is characterised by a rapid evolution and extensive body involvement and marked toxemia, while the moderate type by slow evolution, less generalised eruption and low or no toxemia.

Lesions in pemphigus vulgaris are flaccid bullae arising on normal skin and healing without scarring. Mucous membrane involvement is the characteristic feature of this type. Oral lesions are often the first to appear and the last to heal. Lesions on the palms and soles occur late in the disease and carry a grave prognosis.

Pemphigus foliaceus and pemphigus seborrhoecus are more benign and have a chronic course. The primary lesion is a flaccid bullae, adherent in the center with circinate or polycyclic edges on an erythematous base. Verrucoid plaques with greasy adherent crusts are often noticed in the seborrhoecus type. Butter-fly area of the face, scalp, midchest and interscapular regions are most often involved in both the types. Foliaceus showed a tendency to generalised spread while seborrhoecus is a localised disease. Mucous membrane involvement is conspicuous by its absence.

Clinical transformations from the foliaceus to the seborrhoecus type and the reverse are frequently encountered. These are not observed in the vulgaris type.

Histopathological findings can be broadly divided into two group. Pemphigus vulgaris is characterised by suprabasal clefts with predominance of less keratinized acantholytic cells. These cells show large vesicular non-condensed nulei, with perinuclear halo and basophilic cytoplasm. Barring 5 exceptions pemphigus foliaceus and seborrhoecus showed a more superficially located cleft, the acantholytic cells are more keratinised and dyskeratosis was encountered in one case of each type. These acantholytic cells show pyknotic nuclei, without perinuclear halos, and eosinophilic cytoplasm.

It is suggested that differentiation in the types of acantholytic cells can be used as an index of prognostication and for more accurate determination of the type of pemphigus.

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