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Case Series

Dermatology Section

A Case Series of Recalcitrant Pemphigus

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ABSTRACT

Pemphigus consists of a group of life threatening autoimmune bullous disorders characterised by flaccid blisters and erosions of the skin and mucosal membranes of oral, laryngeal, conjunctival, pharyngeal, anal, vaginal etc. Pemphigus vulgaris involves mucosa in 50-70% of the patients. Pemphigus is associated with other autoimmune disorders like myasthenia gravis and thymoma. Primary subsets of pemphigus include pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. Pemphigus vulgaris constitutes nearly 70% of cases of pemphigus, with its antigens desmoglein 1 and 3, which are calcium dependent calmodulins, being the crucial targets for IgG1 and IgG4 classes of antibodies. If left untreated at an early stage, pemphigus vulgaris is associated with significant morbidity and mortality. The authors present a case series of five patients (34-year-old male, 68-year-old male, 52-year-old male, 74-year-old female and 65-year-old female) presenting recalcitrant pemphigus with focus on the various factors that affect the disease outcomes, morbidity and mortality.

Keywords: Deep vein thrombosis, Pemphigus vegetans, Resistant pemphigus, Septicaemia

INTRODUCTION

Pemphigus vulgaris is an autoimmune genetically predisposed intraepithelial blistering disease that affects the skin and mucous membrane. Pemphigus is noted for its chronicity, characterised by IgG class autoantibodies to the Intercellular Adhesion Molecules (ICAM) viz., desmoglein 3 and desmoglein 1 resulting in loss of cell adhesion and formation of intraepidermal cleft [1].

The prevalence of pemphigus vulgaris in India is 0.09-1.8%. As far as Indian patients of pemphigus vulgaris are concerned, they are said to be relatively younger than their western counterparts [2].

Primary lesion of pemphigus is a flaccid blister that arises on healthy skin or over an erythematous base. Blisters are fragile and filled with clear fluid. Acantholysis, apoptosis, and apoptolysis [3] are the molecular mechanisms that give rise to "row of tombstone" appearance in the routine haematoxylin and eosin (H&E) sections of biopsy and "fishnet pattern" in direct immunofluorescence.

Mucosal involvement occurs in 50-70% of cases. Deaths are common within the first five years of life since the diagnosis of pemphigus vulgaris is made, and if the patient could survive this crucial period, prognosis is really good.

Pemphigus vulgaris is associated with a three times higher mortality rate compared to the general population. It is a potentially life-threatening disease with a mortality rate of 5-15% [4]. Morbidity and mortality are related to age of onset of the disease, extent of body surface area involved, co-morbidities of the patient and the daily dose of systemic steroids or other equivalent immunosuppressives needed.

Although the Dermatologist's armamentarium is equipped with a wide array of therapeutic options ranging from simplest systemic steroids to biologicals [5], biosimilars [6], and biobetters [7], there are still sizeable number of patients who pose a great challenge to the treating Dermatologists by frequent episodes of relapses. The present case series focuses on such refractory patients of pemphigus vulgaris with an insight to find out various factors that affect the disease outcomes, morbidity and mortality.

CASE SERIES

Patients with immunobullous disorder of pemphigus vulgaris attending bulla clinic in a tertiary care centre after confirmation of diagnosis by biopsy and other relevant investigations, were considered for the case series, in whom duration of single episode of pemphigus vulgaris lasted for >3 months, in spite of treatment with steroids and other steroid sparing immunosuppressive agents. The Helsinki guidelines were followed duly. After applying the inclusion and exclusion criteria, the following five patients (three males and two females) were chosen for the present case series [Table/Fig-1]. The study was conducted between May 2021 and October 2021 and the patients are being followed-up till date. The study was approved by the Institutional Ethics Committee (IEC NO.25042021).

Inclusion and Exclusion criteria: Patients of biopsy proven pemphigus vulgaris aged >18 years, both genders, who needed more than 10 mg/day of tab. prednisolone or 2 mg/kg/day of tab. azathioprine for control of disease activity and who were willing to follow-up were included in the study. Patients with active Human Immunodeficiency Virus (HIV), Tuberculosis (TB), Hepatitis B/C virus infections and those not willing to participate/come for follow-up were excluded from the study.

Recalcitrant or resistant pemphigus is defined as recurrent blister formation in spite of immunosuppressive therapy with corticosteroids >10 mg/day of tab. prednisolone or tab. azathioprine 2 mg/kg/day or equivalent immunosuppression [8]. The details of patients of recalcitrant pemphigus has been discussed below and tabulated [9] [Table/Fig-1].

Case 1

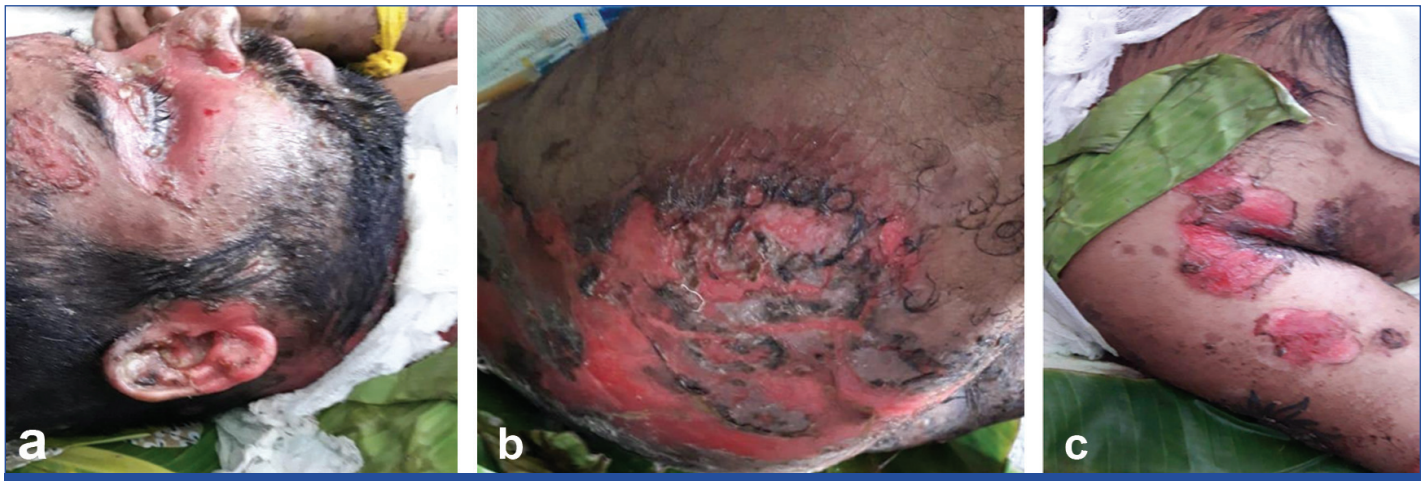
A 34-year-old male who is a known case of pemphigus vulgaris since two years, on conventional treatment with steroids and other immunosuppressants like tab. azathioprine, with no known co-morbidities, came with extensive erosions all over the body. Patient gave history of new vesicles and erosions all over the body after which he applied neem paste and siddha medications, that complicated the pre-existing insult. Patient was started on Inj. methylprednisolone 1 g for three days as pulse therapy and drastic clinical improvement was seen after first cycle. Now the patient is on remission with tab. azathioprine 50 mg OD [Table/Fig-2a-c].

Case 2

A 68-year-old male, a case of recalcitrant pemphigus, came with extensive erosions of three weeks duration. The patient developed extensive erosions involving >80% body surface area mimicking Toxic Epidermal Necrolysis (TEN). Few erosions were also affected with myiasis due to neglected care. Patient finally landed up in sepsis

Age (in years)/ Gender	Duration (in years)	Mucosal lesions	Cutaneous lesions	ABSIS score [9]	Co-morbidities	Time interval between onset of blister and 1st reporting to derm OPD	Past treatment	Treatment started after admission to our hospital	Current status of patient/post discharge follow-up duration (in months)
Case 1 34/M	2	+	+	97	None	4 weeks	Tab. prednisolone 15 mg OD and Tab. azathioprine 100 mg OD	Inj. methylprednisolone pulse×3 days and higher antibiotics	On remission with Tab. azathioprine 50 mg OD/6 months
Case 2 68/M	2.5	+	+	164.5	SHT	3 weeks	Tab. prednisolone 40 mg OD and Tab. azathioprine 100 mg OD	Inj. methylprednisolone pulse×3 days and higher antibiotics	Succumbed to sepsis and MODS
Case 3 52/M	3	+	+	71.75	SHT	2 weeks	Tab. prednisolone 15 mg OD and Tab. cyclophosphamide 50 mg OD	DCP×6 cycles	On remission with Tab. cyclophosphamide 50 mg OD/4 months
Case 4 74/F	2	Laryngeal erosion presenting symptom	Presented 7 months later over scalp and neck	92	Type 2 DM	1 week	DCP×4 cycles, Tab. cyclophosphamide 50 mg OD	Inj. methylprednisolone pulse×3 days	Succumbed to DVT and PTE
Case 5 65/F	2.5	+	+	43.5	Type 2 DM/SHT	4 weeks		DCP×3 cycles	On remission with T. prednisolone 10 mg OD and Tab. azathioprine 50 mg OD/6 months

[Table/Fig-1]: Details of recalcitrant pemphigus patients.
DM: Diabetes mellitus; SHT: Systemic hypertension; DCP: Dexamethasone cyclophosphamide pulse; Inj: Injection; OD: Once a day; MODS: Multiorgan dysfunction syndrome; DVT: Deep vein thrombosis; PTE: Pulmonary thromboembolism



[Table/Fig-2]: Case 1- a) Extensive face lesions with scaling and crusting over the eyelids; b) Extensive erosions over the gluteal area due to constant pressure effects; c) Extensive erosions and raw areas over the right arm and adjoining axillary intertriginous areas.

and multi-organ failure which resulted in death of the patient, inspite of treating him with inj. methylprednisolone 1 gm for three days as pulse therapy [Table/Fig-3a,b].

[Table/Fig-3]: Case 2- a) Extensive skin denudation over the face including periocular, perioral area, maxillary areas of cheek and Ramus of mandible- sites prone for recalcitrant pemphigus; b) Extensive skin separation over trunk giving it TEN-like appearance.

Case 3

A 52-year-old male, known case of systemic hypertension and recalcitrant pemphigus came with extensive erosions especially over the back and scalp of two weeks duration. The patient had assumed hunchback posture due to extensive erosions, that interfered with normal routine activities of life and maintaining erect posture. Patient had remission with six cycles of Dexamethasone Cyclophosphamide pulse therapy. The patient is now on tab. cyclophosphamide 50 mg OD with no new lesions [Table/Fig-4a-c].

Case 4

A 74-year-old female, known case of pemphigus vulgaris since two years and known case of diabetes mellitus on oral hypoglycaemic agents, came with multiple erosions over back, chest, anterior neck of one week duration. This patient had preceding history of laryngeal ulcer two years ago, biopsy of which showed non specific laryngeal mucosal ulceration. Six months later patient developed multiple flaccid blisters and erosions involving back, chest, anterior neck.

Patient developed Deep Vein Thrombosis (DVT) during hospital stay and was started on treatment for the same as per vascular surgeon's opinion with regular monitoring of prothrombin time/ partial thromboplastin time/international normalised ratio. The patient was discharged after resolution of skin lesions, but unfortunately developed pulmonary thromboembolism, two weeks after discharge since she lost to follow-up with vascular surgeon [Table/Fig-5a-c].

Case 5

A 65-year-old female, known case of pemphigus vulgaris and type 2 diabetes mellitus/hypertension came to us with non healing erosions over bilateral axilla. The patient gave history of long standing papillomatous lesions in axilla that were subjected to biopsy outside, which later led to non healing erosions. This patient

[Table/Fig-4]: Case 3- a) Extensive scalp lesions with scaling and crusting; b) Lesions over left underarm with adherent layer of necrotic skin; c) Severe lesions over back with hunchback posture.

[Table/Fig-5]: Case 4- a) Organising epithelial debris with skin denudation affecting neck and right anterior chest -fertile base for vegetans lesions; b) Heaped up lesions with skin denudation and adherent crusts affecting neck- close-up view; c) Raw area over gluteal region, resistant to heal because of pressure effects.
[Table/Fig-6]: Case 5- a) Non healing ulcer following biopsy of pemphigus vegetans lesions in axilla, with secondary infection; b) Haemorrhagic necrotic epithelial debris, with adherent crusting-neck and axillary flexures. (Images from left to right)

received three cycles of Dexamethasone Cyclophosphamide Pulse (DCP) pulse and is now on remission with tab. prednisolone 10 mg OD and tab. azathioprine 50 mg OD [Table/Fig-6a,b].

DISCUSSION

Pemphigus vulgaris has the preference for certain anatomical areas namely scalp, face, neck, upper chest and back. The disease is characterised by great variations in the duration of each episode of illness and also duration of illness as a whole. Factors influencing the chronicity of the illness which also predispose to recalcitrant pemphigus are the following namely [10-12].

1. Anatomic loci involved
2. Severity of the initial disease
3. Oral involvement
4. Presence of both desmoglein 1 and desmoglein 3
5. Early age of onset

Certain races like the Ashkenazi jews and Asian ancestry can predispose to recalcitrant pemphigus.

Common sites of involvement (cutaneous and mucosal) seen in the present cases that can predispose to recalcitrant pemphigus are :

1. Extensive lesions involving malar area of cheek [Table/Fig-2].
2. Periocular
3. Perinasal
4. Perioral [Table/Fig-3a,b]
5. Scalp- extensive areas of involvement causing loss of hair, secondary scaling and fissuring that heals with post inflammatory hypopigmentation. Scalp is a unique site for pemphigus due to the abundance of desmogleins located in hair follicles [Table/Fig-4a] [13].
6. Jawline- involving skin over ramus of mandible, extending into anterior and lateral aspect of neck [Table/Fig-3].
7. Oral mucosa- pain resulting out of mucosal involvement causes odynophagia/dysphagia interfering with normal feeding habits/ fluid intake precipitating malnutrition. Superadded candidiasis adds to the pain and soreness during swallowing.
8. Anal and perianal mucosa- makes patients prone for painful bleeding fissures and perianal fistulae.
9. Laryngeal mucosa- causes hoarseness of voice and incoherent speech.
10. Presternal area: Takes longer time to heal and interferes with chest expansion. Corresponding involvement of extensive areas of the back may lead on to hunch back posture (pseudo kyphosis), that prevents patients from even assuming a proper erect posture [Table/Fig-4b,c].
11. Involvement of Neck: anterior and lateral aspects, interfering with normal flexion and extension of neck [Table/Fig-5a-b].
12. Groin involvement, wherein the intertriginous lesions, of thigh on maceration and friction leads to vegetans lesion.
13. Pressure or weight bearing areas, like gluteus maximus muscle, if involved, can give rise to bed sores that are very resistant to heal [Table/Fig-2b,5c].

Involvement of flexural areas or so called intertriginous areas predisposes the patient to the variant of pemphigus vulgaris called pemphigus vegetans [Table/Fig-6a] [14]. The constant maceration of skin because of opposing nature of intertriginous areas, inadequate removal of debris, crusting resulting out of seropurulent discharge in the intertriginous areas favour the formation of papillomatous lesions [Table/Fig-6b] [15].

The Neumann type almost starting as a blister followed by erosions like that of classical pemphigus vulgaris also has a protracted course like that of pemphigus vulgaris.

The Hallopeau type which starts as pustule has a more benign course heals faster unlike Neumann type [14]. The biopsy of papillomatous lesions in the intertriginous areas leads to long standing non healing erosions, post biopsy, like in our patient-case 5. These fleshy lesions in intertriginous areas are extremely resistant to topical treatment like saline soaks/potassium permanganate soaks [Table/Fig-5].

In our clinical practice, we commonly encounter patients presenting with cutaneous and mucosal lesions at the same time wherein diagnosis of pemphigus vulgaris will be of no challenge. But few patients, as in case 4, can present with exclusive mucosal erosions

involving larynx without any cutaneous lesions which on biopsy shows non specific mucosal ulceration delaying patient from taking an expert opinion from Dermatologists. A high degree of suspicion is needed in this stage to diagnose mucosal pemphigus.

It is observed that a patient can have exclusive mucosal lesions of pemphigus for a period of six good months before development of classical cutaneous lesions [16].

Possible factors affecting disease activity and hence, predicting proneness for recalcitrant pemphigus :

1. Body Surface Area involved (ABSIS Score) and average dose of steroid needed to control disease activity-

   Any patient with > 20% body surface area, with involvement of two or more anatomic loci that could predispose to recalcitrant pemphigus is of crucial importance, as it warrants longer duration of treatment with immunosuppressives. ABSIS score serves as a tool, and the dose of steroid if >10 mg/day is a cause of concern.
2. Direct Nikolsky's sign- following initiation of treatment , out of marginal Nikolsky and direct, it is marginal Nikolsky that takes longer time to become negative. Also, presence of pemphigus paronychia is an indicator of activity of the disease.
3. Age of the individual- earlier the age of onset, the disease has a protracted course.
4. Co-morbidities- like obesity, diabetes mellitus, systolic and diastolic hypertension, dyslipidemia, association with other autoimmune disorders like thymoma and hashimoto's thyroiditis will naturally prolong the duration of the ailment.
5. Duration of the disease- greater time interval between the onset of first lesion of pemphigus vulgaris and patient's arrival at the OPD is of huge significance as more the delay, more will be the titre of circulating autoantibodies.

In all the above five patients, the control of disease activity (defined as the time at which occurrence of new lesions ceases and already existing lesions begin to heal) and end of consolidation phase (defined as the time at which no new lesions have developed for a minimum of two weeks, and approximately 80% of lesions have healed) [17] were not attained within the order of few weeks, which is the normal expected course of the disease activity from the day therapy is started by the physician, thereby enabling us to justify the terminology of recalcitrant pemphigus.

6. Prior to arrival at the Dermatology Outpatient Department, application of indigenous medications like: neem/turmeric paste, as in case 1, due to assumption of pemphigus lesions as chickenpox complicates the situation where the added insult of irritant contact dermatitis paves the way for sepsis.

Causes of Death

1) Disease related:

- Extensive involvement of skin and mucosal surfaces makes way for superadded infections,cutaneous myiasis due to loss of barrier functions of skin.This leads to septicaemia and therefore, multiorgan failure.

Mucosal involvement causing dysphagia, odynophagia and bleeding from gastrointestinal tract, compromise in the lumen of hollow viscera can add on to the already existing insult.

- Bronchiolitis obliterans can many a times be an important lethal terminal event in long standing patients of pemphigus vulgaris, which unfortunately goes undetected.
- Extensive denuded areas will lead to seropurulent/serosanguinous discharge which will induce resistance to topical agents used in treatment [Table/Fig-6b]. Also, pre- existing sero-sanguinous discharge will lead to heaping up of epithelial debris that over a period of time goes in for firm adherent concreting debris [Table/Fig-6a], acting as space occupying lesion preventing new viable epithelial cells coming up to bridge up the erosions or favours papillomatous three dimensional projections in intertriginous areas leading to the recalcitrant variant of pemphigus vegetans.

Hence, its mandatory to have adequate saline or potassium permanganate soaks to remove debris periodically. Because of extensive involvement of skin and mucosa, there will be prevention of normal mobility, especially in elderly individuals, to accomplish day to day tasks of life. Such prolonged immobilisation in elderly individuals especially with co-morbidities makes them prone for DVT due to sluggish flow of blood. The worst sequelae of DVT is throwing of an embolus into the crucial areas of circulation like pulmonary or central nervous system. It becomes mandatory for the treating Dermatologist to add an appropriate antiplatelet or anticoagulant, wherever it is warranted, with its accompanying compulsion of monitoring Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalised Ratio (INR).

In the present study, the authors have lost a patient, who was successfully brought out of recalcitrant pemphigus, but was highly unfortunate to lose the same patient to pulmonary embolism that was thrown out of a DVT (Case 4).

It is important to mention that aspirin given as an antiplatelet agent can precipitate pemphigus vulgaris, as it contains phenol group [18]. Hence, safer alternatives like clopidogrel or rivoroxaban can be tried. Drugs like Warfarin, if prescribed, may warrant the necessity to monitor INR.

2) Treatment related:

- Opportunistic viral infections like herpes zoster and disseminated herpes due to long term use of systemic immunosuppressants.
- The preservatives used in ophthalmic antibiotic drops used for ocular involvement can cause Stevens-Johnson Syndrome (SJS) which can further worsen the lesions.
- Any of the co-prescription that the patient has taken can induce SJS/TEN [Table/Fig-3], which will further deteriorate the general condition of the patient. Because of massive areas of skin necrosis pseudo NIkolsky becomes positive and massive epidermal peeling will add on fuel to fire of the pre-existing pemphigus erosions.
- Prolonged immunosuppression, that too in patients with co-morbidities like diabetes, treated pulmonary/extrapulmonary Koch can precipitate a full blown septicaemia where the patient finally lands up with multiorgan failure, being the terminal event in the trail of an agonising course of the disease.

Treatment Considerations

The presence of overt or occult sepsis can decrease the therapeutic efficacy of steroids. This invites one more immunosuppressant drug, hence, increasing the quantum of immunosuppression.

Mode of administration of immunosuppressant also matters a lot. Pulse dosing of immunosuppressant is found to be of better therapeutic efficacy than daily dosing. Cyclophosphamide when given as pulse dosing (500 mg i.v. once in four weeks) has a cutting edge over daily administration of cyclophosphamide (50 mg tablets once daily) as it impairs immune surveillance for relatively short periods when given as pulse therapy once in 3-4 weeks than when given as daily dosing of 50 mg. Moreover, it doesn't cause myelosuppression to cause immunosuppression.

As far as United States Food and Drug Administration (US FDA) approved dermatological indication of cyclophosphamide is concerned, it is only mycosis fungoides, but when it is used in the treatment of bullous disorders along with dexamethasone in form of dexamethasone cyclophosphamide pulse, it is very instrumental in limiting disease activity and, at the same time ensuring minimal adverse effects of corticosteroids like immunosuppression [19].

Also, it is seen that patients not responding to conventional corticosteroids/immunosuppressants are treated satisfactorily with injection methylprednisolone pulse. The commonest adverse effects noted were nausea, gastritis, vomiting, sudden shooting of blood pressure. Hence, monitoring for these symptoms is mandatory.

CONCLUSION(S)

Majority of the patients of pemphigus vulgaris experience relapse and remission during the first five years of disease activity. Any patient who can successfully tide over the first five years of the disease activity is said to have a reasonably good longevity of life and the disease is said to have less mortality rate. Early diagnosis, either when the patient is still in the mucosal phase alone wherein they can stay in this phase for six months or when the lesions are confined to less than 10% of BSA in the case of mucocutaneous variant, and prompt treatment with Immunosuppressants, adequate follow-up, keen interest on factors predisposing to recalcitrant variant, co-morbidities of the patient after maths of the prolonged disease activity like DVT and PTE, has a very huge impact on the prognosis of the patient and successful restoration of near normal DLQI. Particularly in this era of Coronovirus Disease 2019 (COVID-2019) pandemic, to keep a patient on immunosuppressants for a longer time poses one more threat to the treating Dermatologists, wherein contracting COVID-19 infection is always there on the high rise in patients maintained on immunosuppressants for a long time.

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