Symposium - Vesicobullous Disorders

Pemphigus in India

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ABSTRACT

Pemphigus is a chronic epidermal immunobullous disease with potentially fatal outcome. The journey of literature on pemphigus in India has come a long way in last five decades. Pemphigus in Indian patients has unique genetic, clinical, and epidemiological differences from those in the Western countries. Corticosteroids remain the mainstay of treatment for pemphigus. Dexamethasone-cyclophosphamide pulse therapy has revolutionized the management of pemphigus in India and abroad for nearly 3 decades now. Corticosteroid-based treatment, along with adjuvants, has significantly brought down the high mortality rates that had been observed in precorticosteroid era. Present day research is largely based on elucidating the pathogenesis beyond the antidesmoglein antibodies, and newer diagnostic and treatment approaches. In this article, we review various aspects of literature on pemphigus in India, on Indians abroad, or literature from other countries that are considered relevant to the topic.

Key words: Pemphigus, clinical features, diagnosis, management, India

INTRODUCTION

Pemphigus is a chronic autoimmune epidermal bullous disease caused by autoantibodies directed against desmogleins (Dsgs), that is, desmosomal glycoproteins expressed on the epithelial cells of the skin and mucosa, resulting in acantholysis. Recent studies have shown that acantholysis can also occur in presence of antibodies against 9-α nicotinic acetylcholine receptor.[1] Apoptosis of keratinocytes may have a possible role in pathogenesis.[2] Common pemphigus types include pemphigus vulgaris (PV); its variant pemphigus vegetans (PVeg) and pemphigus foliaceus (PF) with its variant pemphigus erythematosus (PE). Recently described variants are pemphigus herpetiformis, IgA pemphigus, and paraneoplastic pemphigus. Though corticosteroids have remained mainstay of therapy for pemphigus, immunoadsorption techniques, intravenous immunoglobulin and monoclonal antibody rituximab have given fillip to effective pemphigus management for severe cases. Indian experience on these newer agents is limited with no published data, and consequently does not form a content of this review.

A PUBMED search (with search terms pemphigus and India) retrieved 96 articles (retrieved August 6, 2010) with earliest one dating back to 1960 in which Desai and Rao had described 21 cases of pemphigus.[3] Literature on pemphigus have flourished subsequently in India. Due to lack of facilities to elucidate the molecular aspects of the disease in most of the centers, Indian literature on pemphigus has largely remained restricted to epidemiology and treatment with some recent research on immunology. In this review, we have discussed epidemiology of pemphigus in India or in patients of Indian origin overseas, clinical features, pathogenesis, diagnosis, complications, and management of pemphigus.

EPIDEMIOLOGY

Epidemiology of pemphigus has shown different trend

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in India compared with Western literature in various counts. The incidence of pemphigus among the dermatology outpatient attendees has varied widely, 0.09 to 1.8%.[4,5] The incidence assessed by clinic-based questionnaire survey conducted in Thrissur district, Kerala, was 4.4 per million population per year. The incidence was found to be higher than available data from Germany, France, and lower than Tunisia.[6]

A majority of pemphigus patients have been diagnosed to have PV, the proportion varying between 75 and 92% of total pemphigus patients.[5,7] Sehgal[7] reviewed 224 cases pooled from 5 studies published from different parts of the country.[8-12] The types of pemphigus that followed PV in incidence are PF, PE, and PVeg, in decreasing order of frequency.[7] In a study assessing IgG subclass in patients from UK and India, the proportion of PV and PF was almost equal in patients from UK, while PV was the predominant type in Indian patients.[13] Similar were the findings in Kwa-Zulu Natal province of South Africa where 43% of studied patients were of Indian origin. Meanwhile, Indians comprised only 9% of the baseline population where the patients were drawn from.[14] Among those patients who had PF, 80% were black natives, while 82% of the PV patients were of Indian origin. These findings testify that pemphigus is common in Indians and PV is the commonest type observed. The earlier the pemphigus appears, more particularly the foliaceus variety, the more is the severity.[15]

A significant proportion of patients have been younger than 40 years of age. This is in contrast to other parts of the World where pemphigus occurs much later, 40 to 60 years being the age when pemphigus first appears.[16] Young patients less than 40 years of age comprised >50% of total patients (51.85%, Mascarenhas *et al*.[4] and 56%, Singh *et al*.[15]), while Sehgal[7] observed 50% of pemphigus occurring between 21 and 40 years of age. The age of youngest patient of Singh *et al's*.[15] series was 7 years, while that of Ambady *et al's*.[9] series was 5 years. Subsequently, Kanwar *et al*. have reported pemphigus in children in two different studies which is in contrast to overall observation that pemphigus rarely occurs in children.[17,18]

The gender predisposition has projected contrasting results. Overall, it appears that both sexes are equally affected, though. The studies reported a significant male preponderance (3 : 1,[7] 3 : 2l[15]) to significant female preponderance (0.8 : 1,[4] 1 : 1.2[5])

The studies reported from North India have reported a higher incidence of pemphigus in patients from poor socioeconomic strata.[8,15,19] This may be due to selection bias; well-to-do patients reporting to private practitioners/hospitals while the studies having been conducted in government hospitals.

ABO blood group B has been found to be most commonly associated with the development of pemphigus.[12] This finding could be due to the highest prevalence of such blood group in the background population where the patients hailed from.

GENETIC SUSCEPTIBILITY AND IMMUNOLOGICAL ASPECT

Genetic susceptibility to pemphigus is apparent from the following facts: it is more prevalent in people from Jewish or Mediterranean ancestry, familial cases, increased prevalence of other autoimmune diseases in the first-degree relatives of pemphigus patients, and detection of anti-Dsg antibodies in asymptomatic parents, etc.[16] Higher incidence of PV and earlier age at onset for pemphigus seen in Indian population have been attributed to higher frequency of DSG3*TCCCC in Indian population. In an association analysis of intragenic single nucleotide polymorphism haplotypes to assess the contribution of Dsg 3 allele in susceptibility to PV, it was observed that two related haplotypes, DSG3*TCCTC and DSG3*TCCCC, were involved in the pathogenesis of PV in patients with British and North Indian descent, respectively.[20]

MHC class II alleles and haplotype frequencies (HLA-DRB, DQA1, and DQB1) in 37 patients with PV and 89 normal relatives from New Delhi and Ahmedabad were analyzed.[21] PV patients had significantly increased frequencies of DRB1*1404, DQA1*0101, and DQB1*0503. Patients from Ahmedabad had a significantly increased frequency of HLA-DQB1*0302. Thus, genetic susceptibility may be important determinant in epidemiological difference of pemphigus in India.

Kumar *et al*. analyzed Dsg 1 and Dsg 3 antibody levels using enzyme-linked immunosorbent assay (ELISA) to correlate between the disease severity and antibody titer.[22] Though Dsg1 and Dsg 3 antibodies were found in all patients of PV and foliaceus, they observed a significant correlation between higher Dsg3 antibody titer and severity of oral involvement and Dsg1 titer and skin involvement, irrespective of the type of

pemphigus. Majority of their patients with PV having resolving disease or disease in remission had high titer ELISA positivity against Dsg 3. This apparent contradiction indicates that titer of pathogenic IgG subclass may be more important in determining disease severity rather than overall IgG titer. In few cases of active PV, Dsg 1 and Dsg 3 were positive in low titer. This could have been due to the causative role of pathogenic antibodies against antigens other than Dsg1/3 or antibodies directed against the intracellular domain of Dsg1/3 that were undetectable to ELISA kit used. In a similar study evaluating antibodies to Dsg 1 and 3 assessed by ELISA in PV patients and correlating the titer with disease expression and severity, the basic findings were similar. Anti-Dsg 3 titer correlated positively with mucosal severity of the disease, while anti-Dsg 1 titers correlated with skin surface area involvement.[23]

Pemphigus being an autoimmune disease driven by autoantibody against epidermal antigen, it is expected from immunological point of view that Th2 predominance would be observed. It has been confirmed by Satyam *et al*. in their study on serum samples from patients of either PV or PF.[24] IL-4 and IL-10, markers of Th2 driven immunity, was overexpressed, whereas IL-2 and IFN-γ, markers of Th1 driven immunity, were significantly suppressed. The underexpression of Th1 cytokines has been explained by suppressive effect of IL-4 and IL-10.

Predominant subclass involved in pathogenesis of pemphigus is IgG_4 irrespective of type of pemphigus, as was assessed by direct immunofluorescence (DIF) as well as indirect immunofluorescence (IIF) study using normal human abdominal skin as substrate.[13] IgG_1 and IgG_4 were most frequently deposited subgroups, whereas IgG_4 was the dominant subgroup having strong deposition. IgG subclasses were not found to be related to type, extent, or severity of disease in PV.[25]

CLINICAL FEATURES

Oral mucosal involvement is considered to be initial manifestation in majority of PV patients. In a retrospective review of 71 cases seen over 7 years, 53.52% patients had their disease onset in the oral mucosa, while 23.94% had onset on skin and oral mucosa simultaneously.[26] The buccal mucosa and the hard palate were the commonest site of involvement, followed by lips, tongue, floor of the mouth, and gingiva in decreasing order of frequency. The cases presented with either erosions or ulcers. Patients sought healthcare facility after mean disease duration of 5.5 months.

Involvement of stratified squamous mucosa, i.e, larynx, esophagus, conjunctivae, urethra, vagina, cervix, and anal canal can occur in severe pemphigus. The incidence of esophageal involvement in Indian studies has varied between 67 and 72%.[27,28] In the later study, acantholysis was observed in 27% of biopsied specimens.[25] Irrespective of the degree of clinical involvement, DIF positivity can be found in tissue taken from any part of the whole length of the esophagus.[29]

Isolated PVeg of the tongue has been described.[30] Pemphigus localized on ocular mucous membrane and presenting as erosive conjunctivitis is rare. Sehgal *et al*. reported one such case where the patient had isolated ocular pemphigus for more than a year.[31] Isolated cervical involvement in PV is also rare and may simulate cervical malignancy clinically and cytologically.[32] Gupta *et al*.[32] have reported a case of a 52-year-old lady who presented with vaginal discharge. Routine cervical cytology displayed atypical cells lying singly as well as in clusters. On subsequent colposcopy, cervical erosions and vesicles were observed, which were consistent with PV. On retrospect, the atypical cells were typical acantholytic cells.

Acral involvement is rare in pemphigus and considered to be poor prognostic indicator.[33] Dyshidrosiform PV with crusted erosions, vesicles and bullae on soles, more severe on the margins, in addition to the lesions on other parts of the body including oral mucosa have been reported. The patient responded well to treatment with prednisolone and cyclophosphamide.[33]

Premlatha *et al*.,[34] in their study of 10 patients with PVeg, observed distinctive changes in the tongue for which they proposed the term "cerebriform tongue." Moreover, they observed deep fissures between the vegetations on the vermilion border of the lips of patients with Neumann type of PVeg, while papillomatous hyperplasia was observed on the same location in patients with Hallopeau type. The authors proposed that the presence of cerebriform tongue may be an important diagnostic sign of PVeg.

Hypopyon sign has classically been described in subcorneal pustular dermatosis. Singh *et al*.[35] have reported such a phenomenon occurring in patients with PV as well as foliaceus. They speculated that neutrophils accumulated in the intraepidermal blisters settle down at the dependent areas giving rise to such a phenomenon.

Postpemphigus acanthomata (seborrhoeic keratosis like changes after healing of pemphigus lesions) was studied by Yesudian *et al*.[36] It occurred in 25% of studied patients (13 of 52 included patients, 10 PV, 3 PF). Most commonly, it was seen over the trunk. Histologically, intraepidermal clefts with acantholysis, acanthosis, papillomatosis, and hyperkeratosis were observed. In one of the two patients subjected to DIF, it was positive. As DIF positivity correlates with disease activity, the authors concluded that these patients should be kept on regular follow-up for potential relapse.

Kanwar *et al*.[37] have observed that peculiar fishy odor may be specific for pemphigus and may be of diagnostic value. The cause of this smell is not known but may be due to colonization of bacteria on the denuded skin. The clinical activity of disease is mainly assessed by appearance of new mucocutaneous lesions or extent of body surface area involvement. Pruritus, though not a usual feature of pemphigus, may be a useful clinical sign of disease activity and may predict relapse.[38] The pruritus subsides once the disease is brought under control.

The newer variants of pemphigus have rarely been reported from India, probably due to lack of infrastructure required for immunopathological tests for diagnosis. Mehta *et al*. reported that herpetiform pemphigus clinically resembled bullous pemphigoid, and the diagnosis was confirmed by intracellular deposit of C3 and IgG in the upper epidermis.[39]

Different diseases have been described in association with pemphigus and these include cryoglobulinemia and cold agglutinin disease,[40] renal cell carcinoma,[41] hyperprolactinemia,[42] and brain abscesses.[43] Individual reports of single cases cannot rule out pure chance in such associations.

DIAGNOSIS

Desai and Rao described two types of acantholytic cells. In type "A" cells, they observed fuzzy basophilic cytoplasm, large noncondensed nucleus, and a perinuclear halo, whereas in type "B" cells, well-defined eosinophilic cytoplasm and a condensed pyknotic nucleus were observed.[3] However, these do not have any prognostic significance.

Role of DIF of the outer root sheath (ORS) in the immunological diagnosis of pemphigus has been established.[44,45] As ORS is the continuation of the epidermis, DIF positivity in the epidermis of a biopsied specimen will be present in the ORS of the plucked hair also. Pemphigus antigen is expressed in whole ORS as well as in dermal bulb matrix.[46] In an Indian series recruiting 20 patients, 17 (85%) had DIF positivity in plucked hair ORS.[45] DIF of skin biopsy specimen taken from perilesional area or upper back (in patients with mucosal lesions only) was positive in all patients. DIF of hair being simple, specific, and noninvasive test, it can be used in place of DIF in biopsied specimen to monitor pemphigus activity.

The role of DIF on Tzanck smear has also been assessed.[47] Overall, 60% of studied patients had positivity on skin biopsy, while it was 40% on Tzanck smear. It was observed that it can be equally sensitive to DIF of skin biopsy specimen in patients presenting early, that is, within 3 months of disease onset (40% *vs* 46.6%). Afterwards, the sensitivity became much less (20% *vs* 100%). Positivity in Tzanck smear DIF was directly proportional to the number of inflammatory cells on the smear. Since Tzanck smear preparation is simple, rapid, patient friendly, requiring no invasive procedure and non-resource intensive, it can be used for immunofluorescence testing for early pemphigus. Since air-dried Tzanck smear kept at room temperature has been found to retain the immune reactivity even up to 10 days, it can easily be transported to centers where facilities for immunofluorescence studies are available.[48]

Role of DIF in diagnosis and prognosis of PV has been assessed.[49] Though DIF correlated fairly well with disease activity, in some patients, DIF continued to be positive even in patients who were in clinical remission. The authors believed that immunological activity persisted even in the presence of clinical remission and could predict a future relapse. Baseline IgG, IgM, and complement levels were higher in those patients who had a subsequent relapse. One interesting finding of this study was that the complement levels tended to rise or reappear prior to a clinical relapse, thus being a better marker of impending relapse.

Both DIF and IIF were performed in 20 cases of PV and 2 cases of PF.[50] DIF positivity was observed in all patients, although IIF with human esophagus as substrate was positive in 82.8% cases only. The authors thus proved the role of DIF in confirming a diagnosis of pemphigus, and IF is complementary to histopathology and not substitute of it in diagnosis of pemphigus.

IIF using blister fluid has been tried and showed comparable results with IIF performed with serum taken from the patient. Blister fluid IIF is easy and simple nontraumatic procedure to perform, can be done alone or to supplement IIF with serum to improve the sensitivity.[51]

TREATMENT

Before 1981, pemphigus was treated with systemic corticosteroids, commonly prednisolone in high dosages, depending on initial severity of the disease.[52] This resulted in serious side effects. The senior author remembers patients of pemphigus in early 1970s in Dermatology wards at All India Institute of Medical Sciences, New Delhi, with adverse effects of corticosteroids like peptic ulcer, diabetes mellitus, Cushing's disease, etc. Patient would succumb to side effects of corticosteroid therapy. Adjuvants used included dapsone, cyclophosphamide, and methotrexate. Some patients were empirically given blood transfusions.

Treatment of pemphigus was revolutionized by Pasricha and Gupta[53] who evolved the concept of dexamethasone-cyclophosphamide pulse (DCP) therapy. The mainstay of literature on treatment of pemphigus from India has largely been restricted to this therapy which Indian Dermatology can consider to be its own. Subsequently, various modifications of pulse therapy and various combinations of corticosteroids and other adjuvants have been tried. Newer agents have remained mostly unevaluated formally due to the cost or unavailability of facilities. DCP regimen is broadly divided into 4 phases. In phase one, patients receive 100 mg (136 mg in some centers including that of the authors') dexamethasone dissolved in 250 to 500 ml 5% dextrose on 3 consecutive days every 3 to 4 weeks. Cyclophosphamide 500 mg is administered as slow bolus on a single day, preferably on day two of dexamethasone pulses. In between pulses, the patients receive 50 mg cyclophosphamide daily. Intervening daily prednisolone or pulse in a shorter interval may be given if disease is very severe to start with or early disease control is required. The patient enters phase 2 when complete disease remission is achieved and intervening corticosteroids are completely withdrawn. The patient continues to receive DCP along with daily oral cyclophosphamide 50 mg for 6 or 9 more months. Subsequently, in phase 3, only oral cyclophosphamide is continued for 12 or 9 more months followed by phase 4 which is treatment-free follow-up period for early detection of relapse, if any. The efficacy of DCP regimen in management of pemphigus has been reported time and again, virtually amounting to prediction of "cure" in pemphigus.[5,54-63] Although Western Dermatology community has remained skeptical about the safety of the regimen, three recent reports from UK, South Africa, and Serbia have found its usefulness.[64-66] Ramam, in his editorial in this very journal, has outlined the way forward for DCP.[67] These include the need to identify the difficult situations in pulse therapy and to evolve ways including required modification in the pulse therapy to circumvent these difficulties, addition of another adjuvant to DCP for those who are not responding to DCP even after reasonable period, to identify patient in the very early stages who would respond early to treatment so as to spare them from unnecessary pulses, omission of daily cyclophosphamide for the first two phase when dexamethasone and cyclophosphamide boluses are being given while giving it in phase 3, pharmacokinetic and immunologic studies on DCP, etc., to improve the understanding of this regimen.

Pasricha *et al*.[55] collated data of 300 patients treated with DCP over a 12-year period, including data of patients from their previous publications from All India Institute of Medical Sciences.[53,56,57] The number of patients with different variants of pemphigus included 255 (85%) for PV, 25 (8%) for PF, 15 (5%) for PE, and 5 (2%) for PVeg. Of the 300 patients studied, 190 completed the active treatment (i.e., phase 3) and were in post-treatment follow-up. Twelve patients died, 61 discontinued treatment due to some reason or the other, while 37 patients were continuing treatment and were in phases 1, 2, or 3 of DCP regimen. Maximum post-treatment follow-up duration was 9 years; 48 patients had post-treatment disease-free period of >5 years, 75 with 2 to 5 years, and 67 with <2 years. Majority of the patients (49%) required 6 or less number of pulses for disease control in phase 1, while only 11% required >2 years treatment. Relapses were observed

in 59 patients; 19 before completing phase 3 of DCP while 40 patients had disease relapse during phase 4. These patients were subjected to second cycle of DCP. Although 9 relapses occurred after second cycle, only 2 relapses occurred after third cycle.

Kanwar *et al*.[58] assessed the long-term efficacy of DCP therapy. The time taken to achieve partial remission, that is, for completion of phase 1 (as was defined for the study purposes) was 4.2 months on an average (range, 2-8 months), while time to complete remission, that is, completion of phase 3 was 24 months (20-32 months). The more the pretreatment severity, the more is the number of DCP required for partial remission. They observed four patterns of remission. In 16.6% of patients, a quick initial response was observed and the intervening oral corticosteroid could be tapered very rapidly. In 44.4% patients, though the initial response was rapid, the patient relapsed as soon as the steroid dose was started to be tapered. In 27.7% patients, the initial response was delayed and required oral steroids for considerably long period and took longer period to achieve partial remission. The rest (11.1%) relapsed on stopping the pulse and required additional DCP pulses. The mean duration of follow-up was 4.2 years (2-12 years) and a significant majority of patients had remission for more than 1 year, around 10% having remission for more than 10 years. The authors concluded, based upon the evidence generated from the study, that it is possible to cure pemphigus.

In a subsequent review of 244 patients who received DCP, Kanwar *et al*.[5] observed that around 60% patients required additional intervening prednisolone in phase 1, while the rest could be treated with DCP alone. The mean number of DCP required to induce disease remission was directly proportional to the initial severity of disease. Those with mild disease required 8.9 pulses, while severe disease required 17.2 pulses on an average for achievement of remission. In a retrospective-prospective study, data of 65 patients were analyzed.[59] Around 30% (19) patients either discontinued treatment in phase 1 or 2 or died. Patients who completed phase 1 (32) required 9.53 ± 3.52 pulses on an average (range, 5- 20) pulses. Majority required 5 to 10 pulses to achieve remission. A majority of patients (58, 89.2%) were also given intervening oral steroids with the aim of achieving early clinical remission.

It has been observed that those patients who were regular in their pulses required less number of pulses to go into clinical remission.[68] DCP appears to be more effective in achieving rapid healing of lesions, long-term clinical remission, and fewer incidences of side effects compared with conventional corticosteroid therapy. However, long-term toxicities of cyclophosphamide, including gonadal toxicity, make it imperative to choose patients carefully for DCP. Such observations have been refuted in a recent study comparing monthly DCP with daily oral cyclophosphamide (DCP+C) (otherwise conventional DCP) and monthly cyclophosphamide and daily prednisolone (CP+P).[69] In the DCP+C group, prednisolone was added after 2 weeks of starting DCP, if the patient continued to develop ≥5 lesions per day. In CP+P group, in addition to monthly single pulse of 15 mg/kg cyclophosphamide, patients received daily oral prednisolone. The starting dose of prednisolone was 1.5 mg/kg/day, which was tapered to 1 mg/kg/day after 2 weeks. After disease remission (significant reepithelialization of at least 80% of lesions), prednisolone dose was tapered by 10 mg every 2 weeks until maintenance dose of 10 mg/day was reached and then continued till study end. Time to onset of treatment effect and time to achieve disease remission was significantly lower in the CP+P group (3.16 weeks *vs* 6.3 weeks and 8.4 weeks *vs* 13 weeks). Incidence of side effects was comparable. The significant side effects in the DCP+C group were dysgeusia, hiccups, palpitation, nail discoloration, bone pain, and urine infection, while that in the CP+P group were nausea, moon facies, flushing, secondary amenorrhea, steroid withdrawal symptoms, and dyspnea secondary to weight gain.

Pasricha and Poonam[70] treated 123 patients over a 5-year study period with modified pulse regimen. The modifications over standard DCP pulse incorporated were (a) use of oral betamethasone on tapering doses according to disease severity in phase 1 (b) systemic antibiotics or antifungals for skin and mucosal lesions, respectively, until disease clearance (c) maintenance of skin and oral hygiene despite active lesions. The oral regimen was supplemented by topical corticosteroids, antibiotics, and antifungal agents, as and when required. These agents cure or prevent local infections that are likely to delay healing of lesions. At the time of reporting, all patients were in remission with post-treatment remission period being >5 years in 62 patients, 3 to 5 years in 41 patients, and less than 3 years in 9 patients. Eleven patients had an episode of relapse that was treated with second cycle of pulse

therapy. No intervening betamethasone was required in 17 patients, while >4 mg/day betamethasone was required in only 5 patients.

Concerns have been raised on the modified regimen. One is over the continued use of antibiotics and antifungals till skin or mucosal lesions, respectively, are healed. Such long-term use of antibiotics may lead to development of antibiotic resistance in the community. Moreover, cost of treatment and risk of side effects also get increased significantly. Ramam[71] realized that such agents should be continued till the infections are cleared and not beyond that. Continued use of oral cyclophosphamide while omitting intravenous boluses in those patients who wished to have children in future has been considered to be safe.[72] However, gonadal toxicity is cumulative dose related and does not depend on mode of administration. Total cumulative dose of 30 g and 12 g are considered to be unsafe in women and men, respectively.[71] Secondary amenorrhea was observed in as many as 85% patients in a study following standard DCP protocol.[64] Ramam[71] believes that both oral and intravenous boluses of cyclophosphamide should be omitted in those who wish to have children.

Rao and Lakshmi[73] used DCP, DAP (50 mg azathioprine replaced cyclophosphamide in the intervening period and no bolus azathioprine was given during pulse), or DMP (7.5 mg per week methotrexate replaced cyclophosphamide during first three phases of pulse) in their cohort of 41 patients. DAP was given to those who did not complete their family. DMP was given to those patients who did not complete phase 1 even after 1 year of treatment with DCP or DAP. Of 30 patients who received DCP, 29 showed good improvement by completing phase 1 after an average 8 pulses. Of 4 patients who received DAP, 3 entered phase 4 and remained in remission for more than 2 years. Two patients drawn from the DCP or DAP group, who received DMP due to inadequate response, entered into clinical remission rapidly and continued to be in phase 4 for more than 3 years. Side effects observed were mostly minor and controllable, except one patient who died during pulse due to suspected myocardial infarction. Transient hematuria was observed in 13 patients receiving DCP.

Monthly pulse cyclophosphamide alone without additional corticosteroids has been evaluated in 19 patients of PV and 1 patient of PF.[74] Of these 20 patients, 12 had severe disease and 8 had moderate disease at the initiation of cyclophosphamide pulse. They were put on monthly cyclophosphamide 500 mg single day pulses after they were considered to be resistant to oral corticosteroids or developed side effects to corticosteroids. Eighteen patients completed the proposed study of 12 monthly pulses followed by 6 bimonthly pulses. Excellent response was seen in 12 patients and the remaining 6 had good response. Fourteen patients remained in remission till the end of 1-year post-treatment surveillance period. Nausea and vomiting were experienced by 8 patients and amenorrhea by 5 of 13 women.

In an international multicenter prospective, randomized, parallel-group, placebo-controlled trial in 21 centers including four centers from India, mild to moderate pemphigus were treated with 2 or 3 g/day mycophenolate mofetil with oral corticosteroid or placebo with oral corticosteroid.[75] Although 94 patients were given treatment, 75 completed the study. Treatment responses occurred in 69% of the treatment group and 63.9% in the placebo group. Although no advantage of mycophenolate mofetil over placebo was observed considering treatment response, initial response was faster and response was longer lasting in mycophenolate mofetil group. The group concluded that mycophenolate mofetil may be potentially useful in mild or moderate pemphigus, based on the improved results of secondary end-points including time taken to initial response and duration of response.[75]

In a single center retrospective evaluation of allogenic hematopoietic stem cell transplant with nonmyeloablative low-intensity conditioning in 9 patients of PV, sustained clinical remission was maintained at the end of mean follow-up period of 4.24 years.[76] Pretreatment average disease duration was 21 months and the patients had been treated with oral as well as topical corticosteroids before stem cell transplantation. Within 24 hours of stem cell treatment, existing skin lesions started to regress. Over continued follow-up, eruption of new skin lesions was less frequent and after 6 months of treatment, eruption of new lesions stopped altogether. Cyclosporine and prednisolone was continued for 6 months, followed by withdrawal of cyclosporine and tapering of prednisolone followed over next month. However, the authors did not mention indication and selection criteria for inclusion of pemphigus patients into the study.

As early as 1970, Singh[12] could find the useful role of blood or "group plasma" transfusion in reducing the requirement of prednisolone for controlling pemphigus. This can be compared with infusion of IVIg for management of refractory pemphigus, which is increasingly being used in present day dermatology practice.

COMPLICATIONS OF TREATMENT

Immediate and long-term complications of DCP have been assessed in 136 patients.[77] Although flushing was the commonest immediate complication observed in 53.4% patients, weakness was the commonest long-term complication experienced by 55.4% patients. Other common immediate side effects observed were palpitation, hiccups, numbness of feet, psychosis, and polyurea in decreasing order of frequency, while rise of blood sugar, headache, sleep disorder, arthralgia, blurring of vision, menstrual disorder, loss of hair, dysgeusia, and nail discoloration were common side effects observed over a long term. Rare short-term complications were diffuse maculopapular rash, shivering, shooting pain along the thighs, soreness of the mouth, conjunctival congestion, breathlessness, unilateral limb edema, and ecchymoses over forearms, while rare long-term side effects were radiological evidence of osteoporosis of hipbones, decreased sex drive, gain in appetite, and hirsuitism. Incidentally, flushing and hiccup as the side effects of DCP were first documented by the senior author.[78,79]

High-dose intravenous corticosteroid pulse can occasionally lead to cardiac complications that may include arrhythmias, cardiac ischemia, arterial thrombosis due to profound hypercoagulability, and even sudden death. Most of these cardiovascular complications occur within first 24 hours of infusion. High-dose corticosteroids in pulse form can lead to acute change in concentration of electrolytes across cell membranes without associated change in the serum; resultant hypopolarization of the membranes predisposes to cardiac conduction abnormalities. Other proposed mechanisms include augmented vascular reactivity to endogenous vasopressors, and even anaphylaxis to infused corticosteroid. In a study involving 30 patients in whom Holter monitoring was performed for 6 hours before, 2 hours during and 16 hours following pulse therapy summing up to 24 hours, 4 had ventricular ectopics including 2 patients who had complex ventricular arrhythmias.[80] Thirty-three percent of the patients had sinus bradycardia that started after 3 to 6 hours of pulse and reached a nadir at 12 to 15 hours after pulse therapy. The authors recommended to use 24-hour Holter monitoring before starting pulse therapy, as even in those patients who had absolutely normal ECG pre-pulse, ectopics had been observed. Though the concern for safe monitoring of pulse therapy cannot be undermined, experience with pulse therapy over the years suggest that it is reasonably safe even on cardiac point of view.

Kumrah *et al*.[81] have assessed the hypothalamo-pituitary-adrenal axis (HPA) suppression in patients of pemphigus on completion of phase 2 of DCP therapy. These patients did not receive oral corticosteroids (only source of corticosteroids was intravenous dexamethasone in monthly pulses) for at least 6 months before hormonal assay. Suppressed HPA function was observed in 55% patients, though clinically obvious hypoadrenalism was not observed in any of these patients. The risk of HPA suppression was higher in those patients who received additional dexamethasone boluses between pulses in phase 1 of DCP. The authors believed that those patients having subclinical hypoadrenalism detected in hormonal assay did not require corticosteroid supplement routinely, but may require them during periods of stress.

Azathioprine-induced drug fever has been observed in a pemphigus patient. The patient developed remittent fever after 3 weeks continuous administration of azathioprine.[82] The fever subsided after discontinuation of azathioprine and reappeared within 8 hours of restarting the drug. Though this finding is not specific for pemphigus, azathioprine should be considered as a cause of fever where other causes are not apparent.

DIFFICULT ISSUES

The association between pemphigus and HIV is enigmatic and has rarely been reported in the world literature. Though clinical characteristics of pemphigus and response to treatment are not modified by HIV,[83] the problem of such association is two-fold. First, the pathogenesis of an autoimmune disease in a situation of global immunosuppression is difficult to explain. Second, in a disease where immunosuppression is main mode of treatment, HIV is unwelcome. Marfatia *et al*. reported a case of PV that did not respond to usual doses of parenteral corticosteroids.[84] After initiation of antiretroviral therapy, the steroid could be tapered off consequent to improvement in skin lesions.

Another situation of dilemma is pemphigus in pregnancy. Pemphigus may develop or worsen during pregnancy, may pose a dilemma for treatment, or may affect the fetal outcome.[85] The outcome of pregnancy may be jeopardized and may result in severe intrauterine growth retardation and stillbirth, neonatal pemphigus of varying severity in the newborn due to transplacental transfer of autoantibodies, or the newborn may escape unaffected.[86] Prednisolone or adjuvants prescribed to the mother may result in placental insufficiency, intrauterine growth retardation, or fetal death. Corticosteroid pulses are also not indicated.[87] Therefore, a fine balance is to be maintained to effectively control the disease activity in the mother while not adversely affecting the wellbeing of the fetus.

There are several issues that should be considered while administering DCP in pemphigus patients. Though it can lead to reactivation of tuberculosis, it can be administered in patients with old healed tuberculosis with caution and with regular follow-up for early detection of reactivation. In patients with active tuberculosis, DCP is contraindicated. Another issue is concomitant diabetes mellitus. Along with usual antidiabetic treatment, one can consider adding 8 to 16 units of regular insulin in the drip to prevent dexamethasone-induced elevation in blood sugar levels. In presence of mild infections including that of skin, DCP can be given under cover of appropriate antibiotics. However, in cases of severe skin infections like carbuncle, cellulitis, necrotizing fasciitis, and systemic bacterial infections, DCP should be avoided till infections are brought under control. Similar is the situation with any viral infection and DCP should be withheld till it is controlled. In cases of chronic viral infections like chronic hepatitis B or C and HIV, DCP should be avoided. DCP is better avoided in patients with cardiac rhythm disorders and ischemic cardiac disease.

MORTALITY IN PEMPHIGUS

In a retrospective review of cases between 1995 and 2001 to ascertain the cause of mortality in dermatology inpatients, the mortality rate was 3.58%.[88] Pemphigus was the commonest cause of mortality amounting to 35% of all such cases. All these patients had more than 70% body surface area involvement and the causes revealed in these patients were extensive skin involvement, septicemia, bronchopneumonia, and electrolyte imbalance.

In a 5-year review of pemphigus inpatients in a North Indian tertiary care center, 10 died of 126 patients, the overall mortality being 7.9%.[89] Body surface area involvement was 30 to 80% with a mean of 54%. Eight of them had septicemia, most common organism isolated being *Staphylococcus aureus* in 4 patients. The other three patients had pulmonary thromboembolism. The authors concluded that extent of cutaneous involvement is the single most important factor leading to death in pemphigus patients, secondary to sepsis due to entry of bacteria through the raw areas.

Mortality in yet another study was only 4%; the causes of death recorded being septicemia in 10 patients, complication of tuberculosis, renal cell carcinoma, cryoglobulinemia, and cold agglutinin in 1 patient each.[5]

CONCLUSIONS

Pemphigus in India tends to occur at a younger age and severer as compared with Western countries. Pasricha's concept of DCP therapy has revolutionized the treatment of this potentially fatal disorder. The DCP therapy has been observed to be useful in several centers in India and recently in studies from Serbia, South Africa, and UK. Early diagnosis and initiation of therapy is essential. Various adjuvants have been used for their steroid-sparing effects. In the Indian context, cyclophosphamide has been extensively been used and observed to be effective. However, it should not be used in younger patients because of its adverse effects on the gonads. Mycophenolate mofetil and azathioprine are also effective. However, mycophenolate mofetil is costly and not affordable by most patients. We have administered IVIg and rituximab in few patients with good results.

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