malar area of the face (Figure 1), back, neck and extremities of 2 months’ duration. Her oral cavity showed non-indurated ulcers. Diffuse and patchy alopecia was observed over the parietal and occipital areas of the scalp.

Investigations showed normocytic, hypochromic anemia, leukocytosis, raised ESR, hematuria, pyuria, and raised levels of total serum bilirubin, serum glutamate pyruvate transaminase and serum alkaline phosphatase. An X-ray chest showed right mid-zone consolidation. Ultrasonography of the abdomen revealed hepatomegaly suggestive of a diffuse parenchymal affection, upper abdominal lymphadenopathy with minimal ascites, and changes suggestive of acute renal parenchymatous disease. Serum HBsAg, Elisa for HIV-1 and HIV -2, serum anticardiolipin antibody (ACA), anti ds-DNA and LE cell tests were negative. Serum anti-Ro test was positive. The serum C3 was 94.3 mg/dl. A skin biopsy showed focal atrophy with keratotic plugging in the epidermis, basal cell liquefaction degeneration with colloid bodies, patchy mononuclear infiltrates in the dermis, and melanin incontinence.

The presence of ANA is one of the criteria for the diagnosis of SLE. In 5-10% of cases of SLE, ANA cannot be demonstrated although the other ARA criteria are fulfilled. About 10% of these cases may eventually become ANA positive. Immunofluorescence (IF) assay or enzyme immunoassay (EIA) can detect ANA. In the IF assays substrates such as Hep2 cells, a human laryngeal cell line, are used. They give a higher incidence of positive results. However, in view of the drawbacks like difficulty of reproducibility and requirement for higher quality control, EIA is a better method for routine use. In our patient, we could eventually detect ANA by using EIA designed by Bio-Rad Laboratories. This is a qualitative immunoassay using tetra methyl benzidine in dilute hydrogen peroxide buffer as substrate. The test was repeated in a couple of other laboratories using the same kit.

Circulating antibodies to DNA are almost always present in active disease, and may occur in the absence of antinuclear factor. Antibodies to soluble cellular antigens include anti-Sm antibody, found in 15-25% of patients with SLE, particularly in patients with renal involvement, CNS disease and vasculitis. Anti-RNP antibody occurs in 25% of patients with characteristics of mixed connective tissue disease. Anti-Ro antibody occurs in 30% of patients who will have increased tendency to photosensitivity, renal disease or Sjögren’s syndrome. Anti-Ro antibody is also found in patients with subacute cutaneous lupus erythematosus (SCLE). In one Indian study, all 7 patients of SCLE were ANA-negative.

The presence of 6 ARA criteria in our patient, along with classical histopathological findings in the skin biopsy, strongly suggest the diagnosis of SLE in spite of the absence of ANA. Hence this case can be labeled as ANA-negative SLE.

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Dexamethasone cyclophosphamide pulse therapy for pemphigus

Sir,
The IJDVL September-October 2003 issue covered various aspects of dexamethasone-cyclophosphamide pulse) DCP pulse therapy.1,2,3

I would like to make the following important points related to DCP therapy:
(1) The duration of infusion of cyclophosphamide pulse:
While the editorial\(^1\) has not discussed this aspect of therapy, Dr. Pasricha\(^2\) has categorically stated that the intravenous drip of dexamethasone and cyclophosphamide should be given over 2 hours. Others have administered this drip over 2 hours\(^3\) or 1 hour.\(^4\) Dr. Balachandran recommends a slower infusion, over 3 to 4 hours.\(^5,6\) These give a false sense of non-standardization of therapy.

As per the manufacturer’s package insert, cyclophosphamide should be infused as soon as possible after reconstitution since there is a possibility of loss of pharmacologic activity. Also its half life is only 7 hours. Hence, it should be given over 1 to 1.5 hours (maximum 2 hours) in order to maintain the maximum blood concentration uniformly over a short time.\(^7\)

(2) Prevention of cyclophosphamide induced sterile hemorrhagic cystitis:
The modification of pulse therapy\(^3\) which advocates an infusion of 500 ml of 5% dextrose on the day of intravenous cyclophosphamide administration needs to be reevaluated. Since patients are frequently diabetic or anemic, and hence in a hyperdynamic circulatory stage, is giving intravenous fluids justified? As a routine ample oral fluid intake is recommended\(^8\) and might suffice.

Administration of the drug should be interrupted at the first indication of dysuria or hematuria.\(^8\) On the day of cyclophosphamide infusion I ask my patients to empty their bladder as frequently as possible, may be half hourly, during the infusion and preferably till 2 hours later.

Cystitis can be reduced in intensity or prevented by the parenteral administration of MESNA, a sulphydryl compound that reacts readily with acrolein in the acid environment of the urinary tract.\(^8\)

(3) Supportive management for prevention of steroid induced osteoporosis: \(^3\)
This should not be called a modification of Dr. Pasricha’s DCP therapy since it is a totally different aspect of comprehensive patient management. If glucocorticoid associated osteoporosis is the main concern, then the bisphosphonate group of drugs (e.g. alendronate), which have emerged as the most efficacious drugs for the prevention of osteoporosis, should be given.\(^9\) Most authorities also advocate a calcium intake of 1500 mg/day in the diet and calcium supplementation and vitamin D intake of 400 IU/day for the prevention of osteoporosis.\(^10\)

(4) Steroids are normally given in a single early morning dose.
While none of the authors have commented on this aspect of DCP therapy, shouldn’t DCP therapy infusions be given in the early morning only?

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Letters to Editor


Dexamethasone cyclophosphamide pulse therapy:
Some suggestions for modifications

Sir,

It was truly enlightening and educative reading the editorial on dexamethasone pulse therapy in dermatology1 and the associated viewpoint by Prof. Pasricha2 who is widely regarded as the father of pulse therapy in India. Pulse therapy has altered the management and outcome of autoimmune diseases in general and pemphigus in particular. It has slowly but surely replaced the conventional dosing schedules for administration of oral steroids. In response to Dr. Ramam’s query (where do we go from here?), I would like to propose the following suggestions for modifications in the time tested though somewhat rigid protocol of pulse therapy:

1. The total duration of treatment may be individualized according to the severity of the disease and response to therapy. So instead of a regimental approach of a total of 18 months for phases II and III, we may rely on a combination of the clinical severity index, immunofluorescence titers and promptness of response to therapy to decide whether to shorten the duration in quick responders and to extend it in slow responders and smoldering cases.

2. The decision to stop pulse therapy after 18 months in phase II + III can be individualized depending on the results of immunofluorescence (IF) tests. This may decrease the relapse rates. The relapse rate is 13-27% if direct IF (DIF) is negative at the end of treatment but increases to 4-100% if DIF is positive. Similarly, the relapse rate is 24% if indirect IF (IIF) is negative and increases to 57% if IIF is positive at the end of treatment.3,4,5

3. Serology by IIF can be replaced by ELISA for direct measurement of desmoglein 1 and desmoglein 3 antibodies.

4. As regards the reservations about the toxicity of cyclophosphamide, it is the cumulative dose that increases the chances of malignancies be it carcinoma of the bladder or hematological malignancies.6,7 A mathematical calculation shows that with a daily dose of cyclophosphamide of 50 mg in phases II and III, the cumulative dose is approximately 25 g. A simple approach to reduce the cumulative dose of cyclophosphamide would be to omit daily administration altogether and replace it with a bolus dose of 500 mg every 4 weeks. The modified phase II would then consist of bolus doses of dexamethasone (100 mg x 3 days) and cyclophosphamide (500 mg on day 2) for 9 months. The modified phase III would consist of only bolus doses of cyclophosphamide 500 mg intravenously every 4 weeks for a further 9 months instead of an oral dose of 50 mg daily. This would reduce the cumulative dose of cyclophosphamide in phases II and III to 9 g only.

5. The bladder toxicity with bolus doses of cyclophosphamide can be further reduced by concomitant administration of MESNA (sodium 2-mercaptoethane sulfonate) given intravenously. This is easily available in India and is given on the day of administration of bolus cyclophosphamide. The usual dose is equivalent to the dose of cyclophosphamide and is given intravenously over 15-30 minute infusions in 5 divided doses over 24 hrs. It acts by binding to the acrolein metabolite which is implicated in causing hemorrhagic cystitis and the subsequent development of transitional cell carcinoma of the bladder.

6. Regarding the management of patients with fulminant disease in whom activity is not controlled in spite of addition of interval pulses and daily steroids, a different approach may be the use of immunoablative high dose cyclophosphamide without stem cell rescue. This approach has been utilized with success in other autoimmune diseases like systemic lupus erythematosus, acquired aplastic anemia and more recently for paraneoplastic pemphigus.8,9,10 It involves use of a high dose of cyclophosphamide