Recently, studies have shown that there is no increase in the incidence of malignancy in childhood herpes zoster.[1] A greater number of patients in the study group had immunosuppression with respect to the control group but the difference was statistically insignificant. Therefore, our study is in concordance with the findings of recent studies. However, our study had a very small sample size to conclude these facts.

In our study, we found a strong significant association between megaloblastic anemia and pediatric herpes zoster. The most common cause of megaloblastic anemia is deficiency of vitamin B_{12} or folic acid. This may be cause of immature immune response leading to low levels of natural killer cells, lymphocytes and cytokines along with virus-specific immunoglobulins which may be the cause of inability to maintain varicella zoster virus latency, leading to appearance of herpes zoster at an early age.[1] However, as our sample size was small, this association cannot be affirmed.

Serology could not be done for detecting antibodies. There may be a possibility of recall and confounding bias. Confounding bias, such as nutritional status of the patients, could have been present. We could not find the underlying cause of megaloblastic anemia.

Despite elaborate literature search, we are unable to find any such study to report the possibility of association of anemia with pediatric herpes zoster. Further prospective population-based studies with better investigation profile and evaluation of nutritional status of these children are required to confirm our observation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Effect of monthly cyclophosphamide pulses on skin sclerosis in systemic sclerosis

Sir,

Systemic sclerosis is a connective tissue disease affecting the skin, blood vessels and internal organs with significant morbidity and mortality.[1] The reduction in skin sclerosis has a beneficial effect on the quality of life and survival of the patients.[2,3] Only very few controlled clinical trials have been performed for the treatment of skin sclerosis due to the rarity of the disease and its highly variable course.[4]

In the present study, we attempted to study the efficacy of low dose cyclophosphamide for a short duration on skin sclerosis in both limited and diffuse types of systemic sclerosis.

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Table 1: Total MRSS before and after pulse

Patient no:	MRSS before	MRSS at end of 6 months
1	12	9
2	17	10
3	16	13
4	25	20
5	25	9
6	13	6
7	20	9
8	5	1
9	21	6
10	17	11
11	30	30
12	20	16
13	5	5
14	17	12
15	21	19
16	29	25
17	22	
18	11	5
19	33	26
20	29	29
21	16	8
22	18	8
23	12	9
24	15	10
25	21	9
26	17	11
27	20	11
28	15	17
29	8	6
30	28	18
31	27	
32	28	22
33	16	6
34	17	18
35	22	11
36	17	10

We did a single-center open-label interventional study at the department of Dermatology at Government Medical College, Kozhikode, Kerala. We included all diagnosed cases of systemic sclerosis as per the American College of Rheumatology (1980) criteria who attended our outpatient department from the period January 2015 through December 2017. Patients with severe systemic organ involvement [grade IV dyspnoea, cyanosis, severe restrictive lung disease (Forced vital capacity of ≤50% predicted) echocardiogram abnormalities, diffuse infiltrative opacities in chest radiography and patients in renal crisis], those on treatment with prednisolone or other immunosuppressive agents and those who have not completed their family were excluded from the study. The study was approved by the institutional research committee and registered with Clinical Trials Registry-India (CTRI/2015/01/005442 dated 22.1.2015) and all the participants signed written informed consent.

All patients were assessed in detail by a thorough clinical examination and the severity of skin sclerosis was evaluated by the modified Rodnan skin score. Complete hemogram, urine routine, liver and renal function tests, random blood sugar, chest radiography, electrocardiogram, ultrasonogram of abdomen and pelvis, skin biopsy and enzyme immunoassay for antinuclear antibody profile, syphilis and human immunodeficiency virus infections were carried out in all patients. Pulmonary function tests, high-resolution computed tomography of the thorax and esophago-duodenoscopy were also performed in all cases.

All patients were admitted and started on intravenous cyclophosphamide 500 mg in 500 mL 5% dextrose over 2 h in the morning. This was followed by 500 mL of physiologic saline solution along with oral hydration to reduce the risk of bladder toxicity. Monthly pulses for six months were given.All patients received supportive treatment including vasodilators. Modified Rodnan skin score was assessed at the starting and the end of the treatment at six months. Sclerosis was assessed separately at different sites before and after treatment. Patients were closely monitored during and after cyclophosphamide therapy for any adverse effects. The statistical analysis was done using the paired *t*-test and Wilcoxon signed-rank test. Continuous data were presented as means ± standard deviation for normally distributed variables.

Of the 36 patients enrolled in the study, 34 were women. The mean age of our patients at the time of presentation was 45 ± 9.7 years (range: 29-67 years). The mean duration of disease was 6 years ± 5.1 years (range: 6 months-20 years). Twenty patients (55.5%) were diagnosed to have limited cutaneous type and 16 (44.4%) diffuse cutaneous type. The modified Rodnan skin score of 36 patients ranged from 5 to 33 with a mean value of 19 ± 6.8 [Table 1].

Out of 36 patients enrolled in the study, two patients failed to complete six months of treatment. The mean modified Rodnan skin score before and after cyclophosphamide therapy at six months was assessed in 34 patients and a significant reduction was noticed from 18.7 ± 6.9 to 12.8 ± 7.2 ($P < 0.001$). Reduction in the modified Rodnan skin score was noticed from two months of starting the treatment.

There was a significant reduction of modified Rodnan skin score in limited cutaneous systemic sclerosis from 16.5 ± 6 to 10 ± 5.2 ($P < 0.001$) and in diffuse cutaneous systemic sclerosis from 21.9 ± 7 to 16.8 ± 8 ($P = 0.003$). Sclerosis at different sites was assessed before and after treatment [Table 2] and we found a significant reduction in mean sclerosis at all sites except on both arms [Table 3]. The right and left forearm and right fingers showed the maximum response.

Table 2: Number of patients and MRSS scores at different sites before and after treatment in 34 patients

MRSS scores	0		1		2		3	
	Before	After	Before	After	Before	After	Before	After
Face	6	7	13	18	10	8	5	1
Anterior chest	27	30	5	4	2	0	0	0
Anterior abdomen	29	33	5	1	0	0	0	0
Right upper arm	24	27	7	5	3	1	0	1
Left upper arm	24	27	8	5	2	1	0	1
Right forearm	2	11	13	14	18	9	1	
Left forearm	3	9	12	16	18	9	1	
Right hand dorsum	9	24	12	6	12	2	1	2
Left hand dorsum	11	23	10	7	12	2	1	2
Right fingers	0	1	1	4	6	13	27	16
Left fingers	0		4	6	5	14	25	14
Right thigh	27	31	4	2	2	0	1	1
Left thigh	27	31	3	2	3	0	1	1
Right lower leg	11	20	12	6	9	6	2	2
Left lower leg	11	20	10	6	12	7	1	1
Right foot	6	18	13	7	12	4	3	5
Left foot	6	17	12	8	12	5	4	4

Table 3: Comparison of mean Modified Rodnan Skin Score at different sites before and after treatment

Site	Mean before treatment±SD	Mean after treatment±SD	*P*
Face	1.4±0.9	1.1±0.8	0.009
Anterior chest	0.3±0.6	0.1±0.3	0.005
Anterior abdomen	0.1±0.4	0.02±0.2	0.025
Right upper arm	0.4±0.6	0.3±0.7	0.366
Left upper arm	0.3±0.5	0.3±0.7	0.527
Right forearm	1.5±0.7	0.9±0.8	0.000
Left forearm	1.5±0.7	1±0.7	0.000
Right hand dorsum	1.1±0.8	0.5±0.9	0.001
Left hand dorsum	1.1±0.9	0.5±0.9	0.004
Right fingers	2.8±0.5	2.4±0.8	0.000
Left fingers	2.6±0.6	2.3±0.7	0.002
Right thigh	0.3±0.7	0.1±0.6	0.025
Left thigh	0.3±0.8	0.1±0.6	0.034
Right lower leg	1.1±1	0.7±0.9	0.005
Left lower leg	1.1±0.9	0.6±0.9	0.003
Right foot	1.3±0.9	0.9±1.1	0.016
Left foot	1.4±1	0.9±1.1	0.002

SD: Standard deviation

The 34 patients were classified into two groups of low modified Rodnan skin score (<18) and high modified Rodnan skin score (>18). In patients with less than 18 score mean modified Rodnan skin score reduced from 13.7 ± 4.1 to 9.3 ± 4.2 ($P < 0.001$). In patients with a modified Rodnan skin score of 18 and more, the mean modified Rodnan skin score was reduced from 24.4 ± 4.6 to 16.8 ± 8 ($P < 0.001$).

Ten out of 13 patients (77%) with dyspnoea and eight out of nine (88.9%) with arthralgia demonstrated improvement of their symptoms. However, there was persistence or exacerbation of gastroesophageal symptoms in a majority (20/22). The incidence of Raynauds phenomenon reduced in 21 out of 26 patients (80.8%), fingertip ulcers subsided in the majority (14/20), recurrence of ulceration on the leg reduced in frequency in six (85.7%) except in one patient and calcinosis in a single patient subsided completely. Though the salt and pepper pigmentation reduced, there was no improvement in diffuse pigmentation and depigmentation in our patients at the end of six months.

Adverse effects included vomiting in two patients, transient elevation of liver enzymes in one patient and temporary amenorrhea in another patient. Cutaneous adverse events included generalized itching in one patient and lichenoid papules in another patient. Gingival hyperplasia was noticed in one of the limited cutaneous systemic sclerosis patients with a positive anti-Scl-70 antibody. Adverse effects were not serious to discontinue treatment.

Our study showed a higher preponderance in women with a female to male ratio of 17: 1 than previous studies.[5] The mean age of 45 years in our patients is much higher than in previous studies.[5,6]

The most common sclerosed site was the fingers followed by the forearm, face and feet. Severe sclerosis of grade three was detected on the fingers in a majority (79.4%) but with less severe involvement on the forearms and dorsa of hands [Table 2].

High dose cyclophosphamide, has been extensively studied for the treatment of systemic sclerosis-related lung disease in three randomized controlled trials but none of the studies evaluated skin scores as the primary target.[7,8]

A high dose of cyclophosphamide carries a heavy risk of side effects and even death has been reported in one of the previous studies.[8] Dexamethasone cyclophosphamide pulse therapy is found to be beneficial but has to be administered for 3 to 4 years.[9] Intravenous cyclophosphamide may be better than oral cyclophosphamide to reduce the cumulative dose and is associated with a lower risk of cystitis, and a lower risk of bladder cancer.[10]

We also attempted to look for site-specific modified Rodnan skin score and compared it with after treatment, when all the sites except both upper arms showed a significant reduction

in modified Rodnan skin score. This finding shows that more severely affected distal extremities responded earlier than less severely affected proximal parts.

Dobrota *et al*. reported that an upper baseline modified Rodnan skin score cutoff value of 18 points is the best indicator of the highest proportion of progressors and the baseline modified Rodnan skin score is the strongest predictor of skin improvement, independent of disease duration.[11] de Macedo *et al*. reported a significant reduction of sclerosis with monthly cyclophosphamide 0.5 to 1.0 g/m^2 IV for 18 months but was done on very high modified Rodnan skin score of above 30, the response could not be differentiated from natural regression.[4] The mean modified Rodnan skin score of our patients being 19, avoids this possibility of spontaneous regression irrespective of treatment. Our patients with modified Rodnan skin score <18 were separately analyzed and found a significant reduction in skin scores after treatment.

To conclude, we found that a relatively lower dose intravenous cyclophosphamide monthly pulse for a short duration is well tolerated and produces a significant reduction of skin sclerosis in both limited and diffuse cutaneous systemic sclerosis. None of the studies so far has attempted to assess the variation of modified Rodnan skin score in LCSS. Low dose cyclophosphamide pulses are effective in reducing the skin sclerosis in patients with low baseline modified Rodnan skin score or milder skin fibrosis who are likely to progress. Our study is limited by the absence of control and open-label study design.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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