

CONTACT POINTS

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Ciclosporin in parthenium dermatitis – a report of 2 cases

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Chembolli Lakshmi¹, C. R. Srinivas¹ and Alamelu Jayaraman²

¹Department of Dermatology and

²Department of Pathology,

PSG Hospitals, Peelamedu,

Coimbatore 641 004, Tamil Nadu, India

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Parthenium dermatitis is known to be mediated by type IV hypersensitivity. We have recently postulated the role of type IV and type I hypersensitivity (1). The air-borne allergen of *Parthenium hysterophorus* not only induces allergic contact dermatitis by type IV hypersensitivity but also perpetuates the dermatitis in sensitized atopic subjects by a type I-mediated hypersensitivity reaction (1). Generation of Immunoglobulin E (IgE) antibodies in response to inhaled or ingested allergens is the hallmark of the atopic immune system with a raised serum IgE seen in 80% of patients with atopic dermatitis (2). Exacerbation of skin lesions of atopic dermatitis is reported after aero-allergen contact (3).

Ciclosporin targets major effector pathways common to both immune-mediated and inflammatory components of various dermatoses (e.g. atopic dermatitis, psoriasis). Its immunosuppressive effect is due to inhibition of interleukin-2 (IL-2) production, whereas inhibition of histamine release from mast cells and downregulation of various cellular adhesion molecules result in a marked anti-inflammatory effect (4). We studied the effect of ciclosporin in 2 atopic patients with parthenium dermatitis.

Serum IgE levels, prick testing, and patch testing results were recorded

before and after initiation of ciclosporin (at a dose of 2.5 mg/kg/day). Prick testing was carried out with parthenium leaf, parthenium antigen extract (containing 500 PNU), glycerinated saline as negative control, and histamine 0.1% W/V as positive control (Creative Drug Industries, Allergy Division, Navi, Mumbai, India). Prick testing using leaves and other parts of the plant 'as is' is an accepted technique in detecting type I hypersensitivity (5). Prick testing using parthenium leaf is reported by the authors (1). Testing was performed on the flexural aspect of the forearm. The maximum wheal diameter was measured after 15 min. To avoid the chance of a false-positive reaction, only values equal to, or greater than, the positive control were considered positive. The intensity of the late phase reaction (LPR) was observed at D 2. Patch testing was carried out with parthenium antigen, parthenium leaf 'as is' and saline (control) using antigens supplied by Systopic Labs, New Delhi, India. The readings were recorded on D 2 and D 4 and results interpreted as recommended by the ICDRG.

Serum IgE was measured by the chemiluminescence immunoassay system (ADVIA Centaur, Bayer Health Care, Mumbai, India). Biopsy of the LPR before and after ciclosporin was also carried out in case II. No other systemic medication was administered 2 weeks prior to and during ciclosporin therapy. Investigations were carried out after obtaining informed consent. Clinical severity scoring (CSS) based on the criteria by Verma et al. (6) was carried out before and after ciclosporin.

Case I

A 49-year-old building contractor presented with severe lichenification and hyperpigmentation of the face and neck associated with intense burning and pruritus of 6-month duration. 13 years prior to presentation, he developed dermatitis over the flexures, which subsequently localized to the

face and neck over the last two years. There was initial seasonal variation with aggravation during the winters, but subsequently the dermatitis persisted with the same intensity throughout the year. He reported aggravation with a burning sensation on exposure to sunlight. History of atopy (allergic rhinitis) was present in the patient. He was treated with azathioprine three years ago for the dermatitis, which was extensive at that time and obtained adequate control over a period of 3–4 months. The results of prick testing, patch testing, and serum IgE before and after initiating ciclosporin are listed in Table 1. Ciclosporin was commenced at 2.5 mg/kg/day (150 mg) and tests were repeated after 10 days. The patient reported dramatic relief from burning and pruritus with ciclosporin monotherapy. He was subsequently given antihistamines and topical steroids. He developed mild hypertension and was treated with amlodipine 5 mg. He was willing to continue ciclosporin despite its cost and his development of mild hypertension.

Case II

A 67-year-old teacher presented with lichenification over the face and neck for two years, associated with intense pruritus and reported aggravation on exposure to sunlight. Other flexures were not involved. Family history of atopy (His daughter had allergic rhinitis) was present. He reported seasonal variation with aggravation in the winter.

Prick testing, patch testing, and serum IgE estimation were carried out before and after initiation of ciclosporin as described above. The results are tabulated in Table 1. Biopsies of the LPR before and after initiation of ciclosporin were compared.

Discussion

Dermatitis caused by *P. hysterophorus* is a chronic and distressing problem in India. Both our patients had an atopic diathesis with a raised serum

Table 1. Results of prick testing, patch testing, Serum IgE estimation and biopsy of LPR before and after ciclosporin

Investigation	Case I (atopy +)		Case II (atopy +)	
	Before ciclosporin	After ciclosporin	Before ciclosporin	After ciclosporin
Clinical severity scoring	34.5	19.5	31.5	10.5
Serum IgE IU/ml, (N-up to 100 IU/ml)	2254.3	1510.4	469.4	373
Patch test				
Reading	+++	+	+++	+ to ++
Constitutional symptoms			Severe	None
Prick test (reading)				
Saline	5 mm	5 mm	3 mm	3 mm
Histamine	8 mm	7 mm	5 mm	5 mm
Parthenium antigen	9 mm	7 mm	5 mm	4 mm
Parthenium leaf	17 mm	10 mm	8 mm	6 mm
Prick test				
Late phase reaction biopsy	Not done	Not done	Leukocytoclastic vasculitis	Perivascular inflammation

N, normal.

IgE. The dermatitis was probably precipitated in the sensitized atopic patients by parthenium. Although parthenium dermatitis is known to aggravate in the summers, the winter may be due to increased growth of parthenium in the months of September, October, and November following the Northeast monsoon showers. Various weed eradication measures have proved unsuccessful. The results of oral desensitization are not consistent (7, 8).

Systemic immunosuppressants like corticosteroids and azathioprine have been used successfully in parthenium dermatitis (6, 9).

Corticosteroids, although effective and widely used, are associated with side-effects. Long-term use may lead to adrenocortical axis suppression with attendant complications. Azathioprine and ciclosporin are used in various immune-mediated diseases as corticosteroid sparing agents. Azathioprine is both an immunosuppressive and an anti-inflammatory agent but has a slow onset of action. Although inexpensive, the time taken to achieve a clinical effect (2–3 months) may cause some patients to discontinue therapy (10). Ciclosporin has prominent anti-inflammatory effect in addition to an inhibitory effect on antigen-presenting cells (Langerhans and dendritic cells), which are pivotal in T-cell stimulation. Significant improvement of atopic dermatitis within 2 weeks of ciclosporin therapy is reported (11). Both our patients reported dramatic relief from intractable pruritus on the tenth day of treatment when both patients were reviewed. Patients developing relapses while on azathioprine also show improvement on initiation of



Fig. 1. Clinical severity before ciclosporin.



Fig. 2. Clinical severity after ciclosporin.



Fig. 3. Patch test reaction before ciclosporin (D 2).

ciclosporin for control of the acute symptoms (unpublished observation).

Marked improvement was observed by reduction in CSS, decreased wheal size following prick testing, and reduction in the severity of the patch test reaction (Figs. 1, 2, 3, 4 – case II). Constitutional symptoms and aggravation of pruritus were observed following patch testing in case II before administration of ciclosporin but were absent when it was repeated while on ciclosporin. The biopsy of the LPR in case II also correlated clinically with a less severe reaction after administration of ciclosporin. This patient also reported that he was able to tolerate exposure to sunlight.

The histopathology of the LPR before ciclosporin showed leukocytoclastic vasculitis (Fig. 5). Pre-formed inflammatory mediators stored in the mast cell granules are responsible for the immediate reaction. The LPR is mediated by newly formed mast cell mediators in concert with inflammatory cells (eosinophils, neutrophils, and lymphocytes) (12). The LPR following prick testing presents as a nodule, which is more painful than itchy, but it can present clinically as dermatitis. Histologically, the LPR is reported to show features of leukocytoclastic vasculitis. There is edema and infiltration of inflammatory cells primarily of eosi-



Fig. 4. Patch test reaction after ciclosporin (D 2).

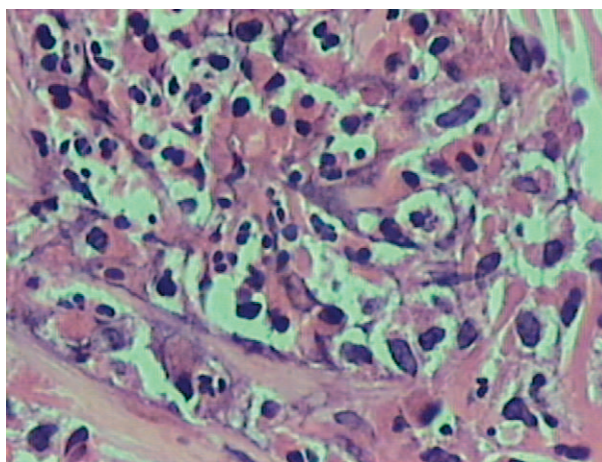


Fig. 5. Biopsy of late phase reaction before ciclosporin showing leukocytoclastic vasculitis. (haematoxylin and eosin stain; original magnification $\times 400$).

nophils and mononuclear cells. Significant vascular damage with hyalinization, fibrin deposition, hemorrhage, or necrosis may also be seen (13). At the peak of the LPR, a more diffuse infiltration of mononuclear cells, neutrophils, and eosinophils may be seen. Immuno histochemical stains show a significant increase in the numbers of mast cells and basophils (14).

Following ciclosporin, the histopathological changes of the LPR were less severe with only a perivascular infiltrate of lymphocytes and eosinophils. There was no evidence of leukocytoclastic vasculitis. Long-term ciclosporin therapy is expensive and associated with side-effects. The dramatic clinical response seen in our patients following 10 days of ciclosporin administration would mean that this drug may also be used as

a crisis intervention measure, as in pustular psoriasis.

Crisis intervention using short-term treatment (4–8 weeks) as in pustular psoriasis overcomes long-term effects of renal toxicity and new-onset hypertension, with minimal risk of adverse effects and restores disease responsiveness to usual treatments (15). Further studies are underway combining ciclosporin with azathioprine in parthenium dermatitis.

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Address:

Dr C. R. Srinivas
 Department of Dermatology
 PSG Hospitals, Peelamedu
 Coimbatore 641 004
 Tamil Nadu, India
 Tel: +0422 2570170, ext. 5220
 Fax: +91 422 2594401
 e-mail: srini_cr_1955@yahoo.com