

Papular dermatitis: response to cyclosporin

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BACKGROUND/AIM: Papular dermatitis is a persistent pruritic papular dermatitis, often refractory to treatment. The objective was to examine the effectiveness of cyclosporin for the treatment of this condition.

METHODS: A retrospective review was conducted of the medical records of a cohort of 16 patients with papular dermatitis who were treated with cyclosporin within the last 2 years.

RESULTS: Twelve of the 16 patients

improved. Of those who improved, two discontinued treatment because of side effects such as hypertension, infection, and tremors. In those that responded favorably, the cyclosporin was tapered slowly. Some patients, however, required continuous therapy due to relapse upon discontinuation of the cyclosporin.

CONCLUSION: Cyclosporin is an effective treatment for papular dermatitis. (*J Dermatol Treat* (2000) **11**: 253–257)

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Introduction

Papular dermatitis (PD) is a subacute or chronic pruritic skin disease of unknown etiology, often refractory to conventional therapy.^{1,2} Also known as subacute prurigo, 'itchy red bump' disease, and papular eruption in black men, PD is the accepted term to describe such patients with similar clinical and histopathologic features. Signs and symptoms include pruritic skin-colored or erythematous papules, with secondary excoriations and lichenification. Histology shows prominent perivascular and interstitial lymphocytic infiltrate in the upper and mid-dermis, with scattered neutrophils and eosinophils, as well as spongiosis.^{1–4}

Clinically, the patients may resemble a number of different conditions including atopic dermatitis, contact dermatitis, dermatitis herpetiformis, scabies, physical urticaria, lichen planus, idiopathic neurogenic dermatitis, pityrosporum folliculitis, and urticarial bullous pemphigoid.

Reported treatments for papular dermatitis have included topical and systemic corticosteroids, and anti-pruritics, anxiolytics, antihistamines, and phototherapy.² Although temporary relief occurs with some of these modalities, long-term results are suboptimal.² Given the success of cyclosporin in treating atopic dermatitis⁵ and psoriasis,^{6–8} we used cyclosporin in patients with papular dermatitis who had failed other therapies. We report here on 16 patients with papular dermatitis treated with cyclosporin.

Methods

The study used a retrospective chart review of a cohort of patients with papular dermatitis who had been treated with cyclosporin during the past 2 years.

Demographic data collection included the age and gender of the patient, duration of skin disease, distribution, history of atopy, previous failed therapies, and response to cyclosporin, as well as side effects (Table I). The patients received cyclosporin at a starting dose of 5 mg/kg per day. Subsequent dosing was adjusted according to response to therapy and the presence of side effects.

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Patient no.	Sex	Age at onset (years)	Duration (years)	Atopic features	Symptom distribution	Patch test/scabies preparations	Failed therapies	Response to cyclosporin
1	M	41	1	–	Scalp, trunk, extremities DG+	–/NT	Antihistamine, antifungals, topical and oral steroids	Improved: pruritus, sustained effect
2	F	44	15	FH: asthma	Neck, trunk, extremities DG–	NA/NA	Phototherapy (PUVA), methotrexate, thalidomide, topical steroids	No response
3	F	75	3	–	Extremities DG–	Potassium dichromate/ NT	Antihistamines, antifungals, topical and IM steroids, trials of d/c and restarting foods	Improved: decreased purpura and pruritus
4	M	60	14	–	Trunk, extremities DG–	–/NT	Antifungals, topical and oral steroids	Improved: decreased no. of lesions and pruritus
5	M	62	5 months	–	Extremities DG–	NT/NT	Antibiotics, topical and oral steroids, dapsone	Improved: decreased no. of lesions
6	F	51	2	–	Extremities DG+	–/–	IM and topical steroids, antihistamines, lindane	Improved: decreased pruritus and no new lesions
7	M	59	7 months	–	Face, chest, lower trunk, extremities DG–	NT/–X2	Phototherapy (PUVA), oral and topical steroids, antihistamine, dapsone, lindane	No response
8	F	67	3	FH: asthma, hay fever	Neck, extremities DG–	–/–	Intramuscular and topical steroids, antihistamine, antifungals, hydroxychloroquine, dapsone	No response

Patient no.	Sex	Age at onset (years)	Duration (years)	Atopic features	Symptom distribution	Patch test/scabies preparations	Failed therapies	Response to cyclosporin
9	M	65	-	-	Extremities	-/-	-	Improved at low dose
10	F	70	8	-	Trunk, extremities DG-	Nickel, epoxy/NT	Phototherapy (UVB), antihistamine, topical steroids	Improved: no pruritus or new lesions
11	M	63	2	-	Face, trunk DG+	NT/NT	Isotretinoin, antihistamine, antifungals	No response
12	M	39	4 months	-	Extremities DG+	NT/-	Antihistamine	Improved: decreased no. of lesions, mild relief of pruritus
13	M	58	4	Hay fever	Trunk, extremities	>40 items/-	Topical steroids, antifungals, antihistamine, benzodiazepines, antibiotics	Improved: decreased thickness of plaques and pruritus
14	F	57	1.5	-	Trunk, extremities	NT/-	Oral prednisone	
15	F	63	1	Eczema, seasonal rhinitis	Neck, trunk extremities	NT/NT	Antihistamine, topical and oral steroids	Improved: decreased no. of lesions and pruritus
16	M	53	8 months	-	Face, trunk	Bermuda grass/-	Antifungals, topical steroids, antihistamine	Improved: decreased no. of lesions

DG = dermatographism; NT = not tested; FH = family history; NA = not available; IM = intramuscular; d/c = discontinued
+ = positive; - = negative

Table 1
Papular dermatitis: response to cyclosporin

The criteria for improvement included self-assessment of pruritus and the extent of skin disease by a patient and physician assessment of the patient's physical findings. While on cyclosporin, monitoring of blood pressure and renal function (urea, creatinine) were undertaken monthly.

Results

Table I summarizes the clinical features of the patients and their response to cyclosporin. There were nine male and seven female patients ranging in age from 39 to 75 years (mean 58 years). The duration of skin disease at presentation ranged from 1 month to 15 years (mean duration of 45.2 months). All patients had been referred by community physicians and had failed multiple therapies. Many had undergone extensive investigations including hematology, chemistry, and serology (for collagen vascular disease), as well as chest radiography examinations in three patients. All these tests were either normal or within normal limits.

Eleven patients had a skin biopsy performed prior to our evaluation, but the remainder of the patients (five) were biopsied at our institution. The descriptions of the histological findings in the 11 patients who had prior biopsies were similar to our findings and showed a predominantly perivascular and interstitial lymphocytic infiltrate containing neutrophils and eosinophils.

Nine patients had biopsies for direct immunofluorescence which were negative. Nine patients were patch tested: four of whom had positive results. The clinical relevance of these was uncertain, however. One patient (no. 13) had an 'angry back' reaction and was not re-patch tested. The other three failed to respond to antigen avoidance. Scabies preparations in eight patients were negative. Serum IgE levels were measured in six patients (patients 1, 8, 10, 11, 13 and 16). In only two patients (patients 10 and 11) were the levels elevated (1260 and 2000 IU/ml respectively).

The patients' predominant complaint was intense pruritus, which often interfered with sleep. On examination, patients had numerous excoriations overlying small papules. Some patients also had secondary dermatitic changes and urticarial-like lesions. All but two patients had lesions on the extremities. Ten of 16 patients had truncal disease. Three patients had lesions on the face, one on the scalp and three on the neck. Four patients exhibited dermatographism. Previously failed therapies included: topical corticosteroids (12), oral antihistamines (11), topical antifungals (seven), phototherapy (three), dapsone (three), lindane (two), antibiotics (two), methotrexate (one), hydroxychloroquine (one), thalidomide (one), isotretinoin (one), and benzodiazepines (one). The combination of dapsone and an antihistamine provided one patient with moderate relief. Five of 11 (45.4%) patients on oral corticosteroids and one patient on intermittent

intramuscular corticosteroids had a moderate short-lived response.

All patients were treated with cyclosporin (5 mg/kg per day): 12 improved significantly with decreased pruritus, decreased number and thickness of skin lesions, and decreased excoriations. Despite initial improvement, cyclosporin was discontinued in one patient secondary to an upper respiratory tract infection. Other side effects led to the discontinuation of cyclosporin in two patients: one owing to increased blood pressure, and tremors and paresthesias of the extremities while the other patient experienced an increase in creatinine, had cyclosporin discontinued and then re-started at a lower dose (2.5 mg/kg per day).

In those responding, improvement occurred within 2 months. Those patients showing a positive response to cyclosporin achieved prolonged results with a gradual taper of the cyclosporin. One patient (no. 1) discontinued cyclosporin after 9 months of therapy owing to complete resolution of the skin disease, with sustained effects 1 year later. Some patients, however, relapsed either upon discontinuation of the cyclosporin or when the dose was lowered. Most of the patients requiring maintenance cyclosporin were controlled on doses of ≤ 2 mg/kg per day.

Four patients had no response to cyclosporin. Side effects in this group included an increase in blood pressure (one), gastrointestinal upset (one) and an increase in creatinine (one).

Discussion

Papular dermatitis is a pruritic dermatitis of unknown etiology, characterized clinically by flesh colored or erythematous papules with secondary excoriations and lichenification, and histologically by a perivascular and interstitial lymphocytic infiltrate. Affected patients are typically refractory to conventional treatments, and disease symptoms of pruritus and dermatitis often persist for years. In our series, treatment with cyclosporin produced a marked improvement in the signs and symptoms of this condition. An initial response rate of 75% (12 out of 16) was achieved; however, continued benefit often required maintenance therapy with low-dose cyclosporin ≤ 2 mg/kg per day).

Cyclosporin is a neutral, lipophilic, cyclic undecapeptide originally extracted from the fungus *Tolypocladium inflatum*. It acts by inhibiting T-cell activation and IL-2 production. Cyclosporin binds the active site of cyclophilin, an intracellular receptor, forming a complex that inhibits the enzyme calcineurin, which is the key enzyme in calcium-dependent signaling processes. Inhibition of calcineurin results in the decreased transcription of cytokines, and interleukin-2 and -4 (IL-2 and IL-4).^{9,10} Impairment of IL-2 production leads to a decline in the proliferation of T-helper cells, cytotoxic lymphocytes and activated CD4 and CD8 cells in the epidermis.¹¹

Patients with papular dermatitis were started on a 5 mg/kg per day dose of cyclosporin, a dose lower than those used in transplant patients (8–16 mg/kg).^{5-9,11-14} The use of cyclosporin for skin diseases has not been associated with an unexpected increase in the incidence of internal malignancies, infection, or seizures.¹¹ None of our patients in this 2-year review developed malignancy or seizures. However, longer follow-up will determine the true safety of this regimen.

The most troublesome adverse effects of cyclosporin include nephrotoxicity and hypertension, which are often dose dependent and have an insidious onset.¹⁵ In cases with hypertension, cyclosporin therapy may be continued in combination with appropriate antihypertensive agents, such as nifedipine and isradipine, which do not lower the serum levels of cyclosporin.^{11,16} Two patients developed hypertension, and each discontinued cyclosporin (Table I).

The nephrotoxic effects of cyclosporin are classified as

functional and structural. Functional changes are secondary to the vasoconstriction of the afferent glomerular arteriole which results in a decrease in the glomerular filtration rate,¹⁰ prompting a decrease or discontinuation of cyclosporin if serum creatinine increases to greater than 30% of the baseline.¹⁷ Structural changes, which are less common, consist of reversible tubulopathy and irreversible vasculopathy.¹⁰ In our cohort, two patients had an elevated serum creatinine: in patient no. 6 the dose was lowered, with return of creatinine to normal levels, and in patient no. 11 where cyclosporin was discontinued due to lack of response to therapy.

We have demonstrated the efficacy and safety of cyclosporin in the treatment of PD and furthermore, in PD patients responding to systemic corticosteroids, cyclosporin provided a relatively safe alternative. However, in light of the potential side effects, cyclosporin's use should be reserved for refractory patients.

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