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Eosinophilic Cellulitis (Wells' Syndrome) Successfully Treated With Low-dose Cyclosporine

Eosinophilic cellulitis (Wells' syndrome) is an uncommon skin disorder. We report two adult male patients who had recurrent erythematous plaques and a nodular lesion on the abdomen. The histopathologic feature of their skin biopsies similarly indicated a marked infiltrate of eosinophils in the dermis with the fashion of "flame figures". One of the patients demonstrated blood eosinophilia. Given the clinicohistological findings, the patients fulfilled the criteria for the diagnosis of eosinophilic cellulitis. The skin lesions remained refractory to medications such as corticosteroids, sulfones, antihistamines, and minocycline. Considering the beneficial effect of cyclosporine in the treatment of eosinophilia-associated dermatoses, we speculated that eosinophilic cellulitis might respond to cyclosporine therapy. Thus, each of the two patients was given cyclosporine (microemulsion formulation) at a daily dose of 1.25 or 2.5 mg/kg, i.e., 100 or 200 mg, respectively. Complete remission of the skin eruptions was obtained in both patients during a 3- or 4-week period of treatment. No side effects were observed. Neither of the patients experienced relapse of the disease at least over 10 months after the discontinuation of the cyclosporine therapy. We suggest that administration of low-dose cyclosporine be a safe and useful therapeutic option in patients with eosinophilic cellulitis.

Key Words : *Cellulitis; Eosinophilic Cellulitis (Wells' Syndrome); Cyclosporine*

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INTRODUCTION

Eosinophilic cellulitis (EC), or Wells' syndrome, was first described by Wells in 1971 (1). EC is an idiopathic rare disorder representing well-circumscribed erythematous plaques with variable appearances, for instances, papulovesicular, blistering and nodular lesions. There are two stages which comprise acute cellulitic and chronic granulomatous. Limbs are the most prevailing sites and trunk is the next. This disorder tends to be episodic and lasts from weeks to months even to years, and heals without scarring (2-4). Histopathologic picture is characterized by a dense diffuse dermal and sometimes subcutaneous infiltrate predominantly composed of eosinophils. Degranulated eosinophilic materials and nuclear fragments are focally deposited around collagen bundles, forming flame figures, which are distinctive but not solely confined to EC (5, 6). In addition, blood eosinophilia is usually present, albeit variable (2, 4). The patients with EC show variable responses to treatment regimens (2-4). Cyclosporine has been used in the management of some immune-mediated cutaneous diseases including hypereosinophilic dermatoses (7-14). Thus, we were encouraged to use cyclosporine in attempts to treat recalcitrant EC. Clearance of the lesions resulted from administration of low-dose cyclosporine within 1 month. To our search, this is the first report of patients with EC successfully treated with cyclosporine. We reviewed the pathogenic role of eosinophils and the usefulness of cyclosporine in EC.

CASE REPORTS

Case 1

A 42-yr-old Korean man presented with reddish swollen plaques, measuring 11×17 cm, on the right lower abdomen (Fig. 1). The lesions were slowly increasing in size, and became more edematous and indurated with localized heat sensation. The eruptions had appeared at the same site several times and had persisted for about 1 to 2 months each time. The patient had no specific medical and family history. He denied taking any drug before the lesions had developed. He had neither previous infection symptoms nor insect bites. He had no previous skin disorders other than chronic urticaria. On examination, there was no palpable lymph node at axillary or inguinal areas. Laboratory investigations including ESR, serum glucose, lipid, liver enzymes, BUN, creatinine, uric acid, and electrolytes were within normal limits. White

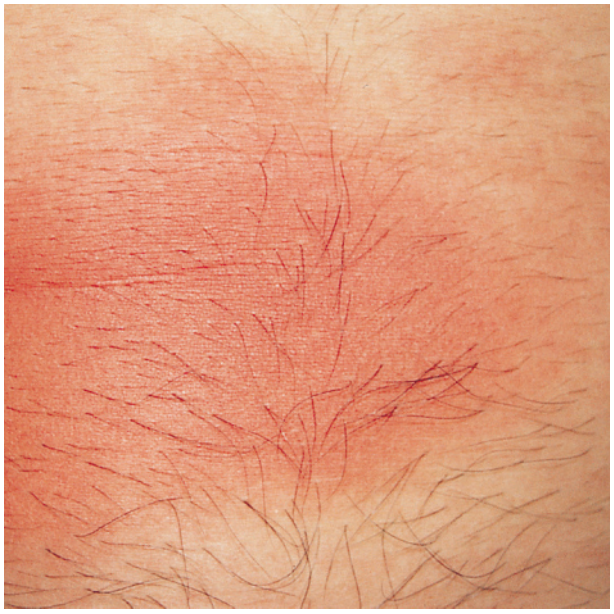

Fig. 1. Reddish swollen plaques, 11 × 17 cm, on the right abdomen (Case 1).

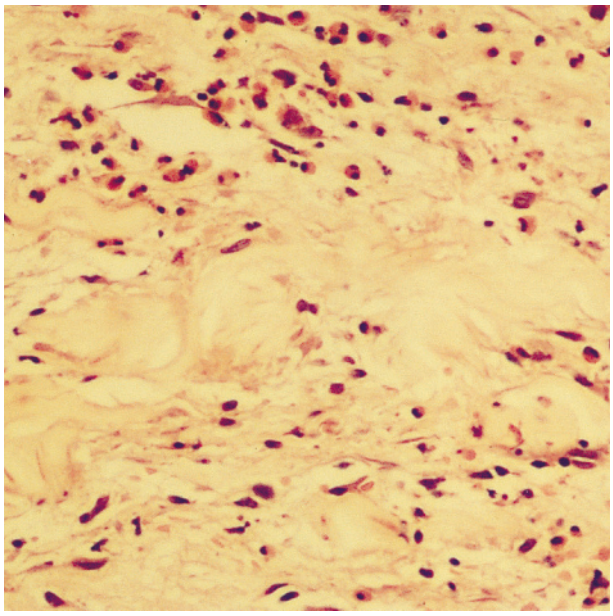

Fig. 2. Diffuse eosinophilic infiltrate with edema in the dermis (H&E, × 250, Case 1).

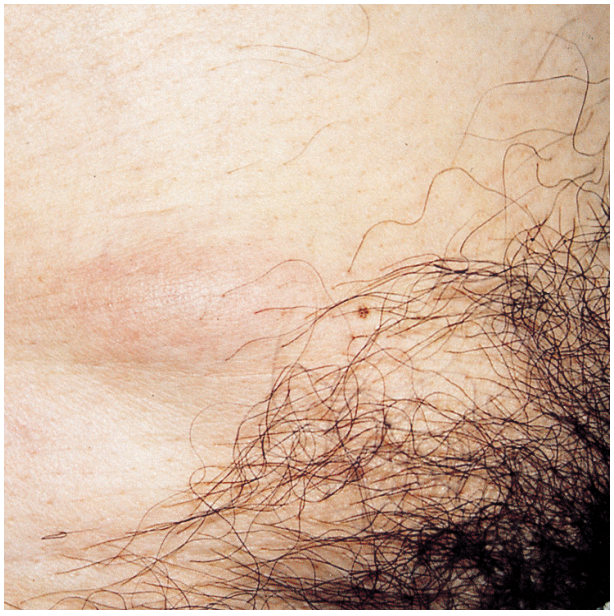

Fig. 3. A gray-blue nodular lesion, 2 × 5 cm, on the lower abdomen (Case 2).

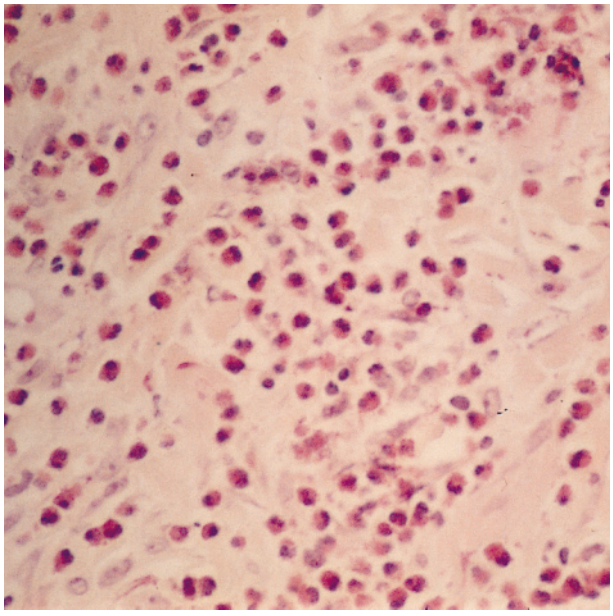

Fig. 4. Dense dermal eosinophilic infiltrate (H&E, × 400, Case 2).

cell count demonstrated mild leukocytosis (12.2×10^9/L, normal range [4.4-10.0 × 10^9/L]) with an eosinophilia (28.6% [0.3-8.0%], eosinophil count 1440/μL [50-500/μL]). Skin biopsy revealed a diffuse inflammatory infiltrate consisting mainly of eosinophils with edema in the whole dermis (Fig. 2). Localized necrotic collagen bundles with eosinophilic granules in the reticular dermis formed flame figures. The patient was commenced on dapsone (100 mg/day) alone for 2 weeks and in combination with cetirizine (10 mg/day) for another 2 weeks, together with potent topical corticosteroid, but with little resolution.

He revisited 4 months later, complaining of the same skin problem. Then, microemulsion cyclosporine was administered at a daily dose of 1.25 mg/kg, i.e., 100 mg, for 2 weeks, by which the skin lesions were significantly improved. With a continuation of the treatment for further 1 week, the lesions

were completely cleared. No relapse has been observed over 12 months after the cessation of the therapy.

Case 2

A 25-yr-old Korean man was referred with an asymptomatic skin lesion of 1.5 yr duration. A single and faintly gray-blue nodule, sized 2 × 5 cm, was observed on the lower abdomen (Fig. 3). According to the history, a reddened swelling had developed which turned gray-blue nodule and then gradually subsided with a residue of postinflammatory hyperpigmentation in 6-8 weeks. The recurrence intervals were 4-6 months on average. Under no established diagnosis, he once underwent an intralesional injection of diluted triamcinolone suspension at a private dermatologic clinic 1 yr ago, with temporary effect. At the time of presentation, he has been suffering from iron deficiency anemia (hemoglobin 7.8 g/dL [12.0-16.0 g/dL]; iron 41 μg/dL [50-130 μg/μL]; total iron binding capacity 503 μg/dL [280-400 μg/dL]) and has been taking $FeSO_4$. Otherwise, no other clinical abnormalities were found, nor any drug was prescribed. White cell count, blood chemistry including glucose, lipid, liver enzymes, BUN, creatinine, and electrolytes were within normal limits except hypertriglycemia (425 mg/dL [10-200 mg/dL]) and increased ESR (46 mm [1-25 mm]). Chest radiography was normal. Skin biopsy showed a dense dermal eosinophilic infiltrate (Fig. 4). Systemic prednisolone therapy (40 mg/day) was started which resulted in no regression of the lesion for 2 weeks. Then, steroid was discontinued. He was given minocycline (200 mg/day) for another 2 weeks, with slight improvement.

He revisited about 3 months later, because of the recurred nodular lesion. Given the remarkable effect in Case 1, microemulsion cyclosporine was immediately administered at the same dose (100 mg/day) for 2 weeks and the lesion partially subsided. The treatment was continued at a daily dose of 2.5 mg/kg, i.e., 200 mg, for further 2 weeks, with complete remission. No evidence for relapse was noted over 10 months after the cessation of cyclosporine.

DISCUSSION

Although the mechanism by which EC develops is still unclear, many factors including viral, bacterial, fungal and parasitic infections/infestations, arthropod and insect bites, myeloproliferative disorders and lymphoma, atopy and urticaria, and drugs are known to be related to EC (2, 4, 5, 15, 16). However, we doubted urticaria or iron supplement for anemia in our cases was connected with the development of EC, in that there was no chronological coherence between these candidate causal factors and the flare-ups of the lesions.

Pathogenesis of EC appears to be linked to the immunobiology of eosinophils (17). Eosinophils are restricted to and activated by cytokine activity from helper T (TH2) cells, which produce interleukin-4 (IL-4) and IL-5. Eosinophils themselves elaborate such cytokines as interleukins, tumor-necrosis factor, platelet activating factor, transforming growth factor, and granulocyte-macrophage colony stimulating factor. IL-5 attracts eosinophils and up-regulates their adhesion molecules. Eosinophils produce cytotoxins such as major basic protein, which contribute to cell membrane damage and eventually cell death (18). A close correlation between clinical activity of EC, eosinophils in blood and bone marrow, and eosinophil cation protein and IL-5 levels in peripheral blood and tissues was described (19). Circulating CD4+ CD7- T cells reportedly play a pivotal role in EC by producing IL-5 (20). Subset analysis of peripheral T cells revealed an increased proportion of CD3+CD4+ cells, suggesting that activated T cells might be implicated in the pathogenesis of blood and tissue eosinophilia in EC (21).

In some patients with EC, oral prednisolone has been of value and topical corticosteroids have been helpful (2, 4, 15, 16). In other patients, dapsone has been given and has provided favorable outcomes (2, 3). Remission was reported in patients treated with a combination of prednisolone, dapsone, and antihistamine (22). There have been data justifying the treatment of patients with minocycline (23), while photochemotherapy (PUVA) has been evaluated to be efficient (24). Not only because these therapeutic options do not necessarily guarantee credible responses but because relapse is apt to follow during the treatment intermission, it is comprehensible that new therapy is required. Typically, our patients had the lesions that proved resistant to the usual treatments.

It is apparent that cyclosporine acts primarily on helper T (CD4+) cells by decreasing their activation, proliferation, and cytokine production (25). Additionally, an effect of cyclosporine on eosinophils and basophils in cutaneous inflammation has given rise to the prospect (26). Cyclosporine has been reported to suppress, in particular, the blood eosinophil counts and the production of IL-5 (27), which fuels speculation that IL-5 may be a therapeutic target in disorders accompanied by eosinophilic inflammation (28).

Cutaneous diseases associated with increased eosinophils include drug-induced eosinophilia (7), hypereosinophilic syndrome (8, 9), eosinophila myalgia syndrome (10), eosinophilic pustular folliculitis (11), eosinophilic fasciitis (12, 13), and angiolymphoid hyperplasia with eosinophilia (Kimura's disease) (14), all of which have already proven dermatologic conditions amenable to cyclosporine. Besides, on the grounds that overlap has been documented (15, 29, 30), it is conceivably presumed that a series of eosinophilic dermatoses may constitute subsets of the wide spectrum of a non-specific eosinophilic hypersensitivity reaction to a variety of provoking stimuli. In this sense, it seemed strange that cyclosporine could never be notified of as one of the treatment options for EC, which rather hightened our inter-

est in using this agent. The assumption that cyclosporine might offer improvement was validated by our trial, rendering its use promising. Nevertheless, further clinical trials are man-datory, since the experience of two cases is not enough to affirm the effectiveness.

Cyclosporine has been used either alone or in combination with other drugs such as corticosteroids. The dose of cyclosporine used in the dermatologic field ranges from 1.25 to 5 mg/kg/day, with a dose of 2.5 mg/kg/day or less tentatively defined as "low-dose"(7-14, 28, 31). Strategies to minimize risk and optimize efficacy have been tailored to usage guidelines in numerous studies. High cost and toxicity/oncogenicity of cyclosporine have limited its prolonged use in chronic cutaneous diseases. With our findings, short-term and low-dose cyclosporine is likely to confer certain advantage offsetting such drawbacks.

Contraindications of cyclosporine include past or current malignancy, uncontrolled hypertension, immunodeficiency, renal insufficiency, and concurrent infection. Hypertension and nephrotoxicity have been addressed as the principal adverse effects (31). A daily dose of >5 mg/kg, persistent elevation of creatinine to >30% of baseline and older age are barometers of the risk factors for cyclosporine-induced nephropathy (32). Oncogenic potential of cyclosporine may raise concerns about an increasing risk of skin cancers and lymphoma (31, 33). It is noteworthy that our patients did not develop hypertension or renal dysfunction during and after the cyclosporine therapy.

We conclusively propose that cyclosporine be granted as a new treatment regimen for refractory EC. Whether to use cyclosporine as the first-line drug in EC remains to be determined.

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