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 instance, 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). 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

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.

Hwan Herr, Jai-Kyoung Koh*
Department of Dermatology, Asan-Foundation Kangnung Hospital, Kangnung, and Asan Medical Center*, University of Ulsan College of Medicine, Seoul, Korea

Received : 2 November 2000
Accepted : 18 December 2000

Address for correspondence
Hwan Herr, M.D.
Department of Dermatology, Asan-Foundation Kangnung Hospital, University of Ulsan College of Medicine, Kangnung 210-711, Korea
Tel : +82.33-610-3207, Fax : +82.33-641-8120
E-mail : herr@knh.co.kr
cell count demonstrated mild leukocytosis (12.2 × 10⁹/L, normal range [4.4-10.0 × 10⁹/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

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).
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 post-inflammatory 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/dL; total iron binding capacity 503 μg/dL; 280-400 μg/dL) and has been taking FeSO₄. 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 hypertriglyceremia (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, micro-emulsion 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/infections, 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 (TH 2) 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), hyper eosinophilic syndrome (8, 9), eosinophilia myalgia syndrome (10), eosinophilic pustular folliculitis (11), eosinophilic fasciitis (12, 13), and angiolymphoid hyperplasia with eosinophilia (K Imura'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 heightened our inter-
Eosinophilic Cellulitis Treated With Cyclosporine

Eosinophilic Cellulitis Treated With Cyclosporine

verse effects (31). A daily dose of
and nephrotoxicity have been addressed as the principal ad-
renal insufficiency, and concurrent infection. Hypertension
malignancy, uncontrolled hypertension, immunodeficiency,
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 ad-
verse effects (31). A daily dose of >5 mg/kg, persistent ele-
dation of creatinine to >30% of baseline and older age are
barometers of the risk factors for cyclosporine-induced nep-
hropathy (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 deter-
mined.

REFERENCES

1. Wells GC. Recurrent granulomatous dermatitis with eosinophilia. Trans St Johns Hosp Dermatol Soc 1971; 57: 46-56.
2. Wells GC, Smith NP. Eosinophilic cellulitis. Br J Dermatol 1979; 100: 101-9.
3. Aberer W, Konrad K, Wolff K. Wells’ syndrome is a distinctive dis-
ease entity and not a histologic diagnosis. J Am Acad Dermatol 1988; 18: 105-14.
4. Goh CL. Eosinophilic cellulitis (Wells’ syndrome). Int J Dermatol 1992; 31: 429-30.
5. Brehmer-Andersson E, Kamann T, Skog E, Frithz A. The histopa-
thogenesis of the flame figure in Wells’ syndrome based on five cases. Acta Derm Venereol (Stockh) 1986; 66: 213-9.
6. Wood C, Miller AC, Jacobs A, Hart R, Nickoloff BJ. Eosinophilic
infiltration with flame figures. Am J Dermatopathol 1986; 8: 186-93.
7. Thomson AW, Milton JI, Aldridge RD, Davidson RJ, Simpson JG. Inhibition of drug-induced eosinophilia by cyclosporin A. Scand J Immunol 1986; 24: 163-70.
8. Zabel P, Schlaak M. Cyclosporin for hypereosinophilic syndrome. Ann Hematol 1991; 62: 230-1.
9. Akiyama Y, Shimizu A, Kimura A, Onodera R, Minatani M, Horikoshi K, Jinga K, Fukakusa M, Kotajima F, Sato T. Successful
treatment of hypereosinophilic syndrome with cyclosporin and steroids. Nihon Kyobu Shikkan Gakkai Zasshi 1997; 35: 541-5.
10. Chau D, Alloway JA, Katz P. Use of cyclosporin A in the eosino-
philic myalgia syndrome. Ann Rheum Dis 1993; 52: 81-2.
11. Taniguchi S, Tsuruta D, Hamada T. Eosinophilic pustular folliculi-
tis responding to cyclosporin [letter]. Br J Dermatol 1994; 131: 736-8.
12. Valencia IC, Chang A, Kirsner RS, Kerdel FA. Eosinophilic fasciitis responsive to treatment with pulsed steroids and cyclosporine.
Int J Dermatol 1999; 38: 369-72.
13. Hayashi N, Igarashi A, Matsuyama T, Harada S. Eosinophilic fasciitis following exposure to trichloroethylene: successful treatment with cyclosporin [letter]. Br J Dermatol 2000; 142: 830-2.
14. Kaneko K, Aoki M, Hattori S, Sato M, Kawana S. Successful treat-
ment of Kimura’s disease with cyclosporine. J Am Acad Dermatol 1999; 41: 893-4.
15. Andreano JM, Kantor GR, Bergfeld WF, Tuthill RJ, Taylor JS. Eosinophilic cellulitis and eosinophilic pustular folliculitis. J Am Acad Dermatol 1989; 20: 934-6.
16. Coldiron BM, Robinson JK. Low-dose alternate-day prednisone for persistent Wells’ syndrome. Arch Dermatol 1989; 125: 1625-6.
17. Lieterman KA. A current perspective on the role of eosinophils in
dermatologic diseases. J Am Acad Dermatol 1991; 24: 1101-12.
18. Sanderson CJ. Interleukin-5, eosinophils, and disease. Blood 1992;
79: 3101-9.
19. Espada A, Sanz ML, Sola J, Gil P. Wells’ syndrome (eosinophilic
cellulitis): correlation between clinical activity, eosinophil levels,
eosinophil cation protein and interleukin-5. Br J Dermatol 1999; 140: 127-30.
20. Yagi H, Tokura Y, Matsushita K, Hanaoka K, Furukawa F, Taki-
wara M. Wells’ syndrome: a pathogenic role for circulating CD4+ CD7- T cells expressing interleukin-5 mRNA. Br J Dermatol 1997;
136: 918-23.
21. Plotz SG, Abeck D, Behrendt H, Simon HU, Ring J. Eosinophilic
cellulitis (Wells’ syndrome). Hautarzt 2000; 51: 182-6.
22. Lee MW, Nixon RL. Eosinophilic cellulitis case report: treatment
options. Australas J Dermatol 1994; 35: 95-7.
23. Stams-Westerveld EB, Daenen S, Van der Meer JB, Jonkman MF. Eosinophilic cellulitis (Wells’ syndrome): treatment with minocy-
cline [letter]. Acta Derm Venereol 1998; 78: 157.
24. Diridl E, Honigsmann H, Tanew A. Wells’ syndrome responsive to
PUVA therapy [letter]. Br J Dermatol 1997; 137: 479-81.
25. Hess AD, Esa AH, Colombani PM. Mechanism of action of cyclo-
sporin: effects on cells of the immune system and on subcellular
events in T cell activation. Transplant Proc 1988; 20(Suppl 2): 29-
40.
26. Teixeira MM, Williams TJ, Hellewell PG. Effects of dexamethasone
and cyclosporin A on the accumulation of eosinophils in acute cuta-
aneous inflammation in the guinea-pig. Br J Pharmacol 1996; 118:
317-24.
27. Wada K, Kaminuma O, Mori A, Nakata A, Ogawa K, Kikkawa H, Ikezawa K, Suko M, Okudaira H. IL-5-producing T cells that induce airway eosinophilia and hyperresponsiveness are suppressed by dexamethasone and cyclosporin A in mice. Int Arch Allergy Immunol 1998; 117(suppl): 24-7.

28. Mori A, Kaminuma O, Ogawa K, Nakata A, Egan RW, Akiyama K, Okudaira H. Control of IL-5 production by human helper T cells as a treatment for eosinophilic inflammation: comparison of in vitro and in vivo effects between selective and nonselective cytokine synthesis inhibitors. J Allergy Clin Immunol 2000; 106S: 58-64.

29. Bogenrieder T, Griese DP, Schiffner R, Buttner R, Riegger GA, Hohenleutner U, Landthaler M. Wells’ syndrome associated with idiopathic hypereosinophilic syndrome. Br J Dermatol 1997; 137: 978-82.

30. Lee SC, Shin SS, Lee JB, Won YH. Wells syndrome associated with Churg-Strauss syndrome [letter]. J Am Acad Dermatol 2000; 43: 556-7.

31. Lim KK, Su WP, Schroeter AL, Sabers CI, Abraham RT, Pittelkow MR. Cyclosporine in the treatment of dermatologic diseases: an update. Mayo Clin Proc 1996; 71: 1182-91.

32. Feutren G, Mihatsch M. Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases. N Engl J Med 1992; 326: 1654-60.

33. Dutz JP, Ho VC. Immunosuppressive agents in dermatology: an update: cyclosporine. Dermatol Clin 1998; 16: 235-51.