A Case of Dermatomyositis Treated with Chlorambucil Combination Therapy

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We herein report a case of therapy-resistant dermatomyositis treated with oral prednisolone and chlorambucil combination therapy. Concurrently, she showed cervical carcinoma in situ(CIS). Initially, we started to treat her with combination oral prednisolone, intramuscular methotrexate, hydroxychloroquin, and removal of cervical CIS. However, our patient failed to respond to these regimens. Thus, we had have another combination treatment of oral prednisolone and chlorambucil. After the treatment of this combination regimen, her recalcitrant dermatomyositis improved dramatically without recurrence. There were no significant adverse side effects with chlorambucil therapy. (Ann Dermatol 11(3) 165~168, 1999).

Key Words : Dermatomyositis, Chlorambucil, Cervical CIS

Dermatomyositis(DM) is an idiopathic inflammatory myopathy with prominent and often characteristic skin disease in which the majority of patients respond to high-dose corticosteroids[1,2]. However, control of the disease can be difficult, and approximately one-fourth of patients with DM either do not respond to corticosteroids or develop steroid-related toxicity[3]. In these patients, alternative therapy with immunosuppresssive agents, alone or in combination with systemic corticosteroids, has proven effective.

We report the successful management of a patient with refractory malignancy associated dermatomyositis, using steroids in combination with chlorambucil after removal of cervical cancinoma in situ(CIS).

CASE REPORT

A 40-year-old woman visited our clinic with general fatigue, myalgia and heliotrope rash around the eyes. Eight months before her visit, the patient noted heliotrope rash around the eyes and poikiloderma on the left upper back with general myalgia. Four months later, she developed progressive proximal muscle weakness and Gottron's lesions on the metacarpal and the interphalangeal joints. Shortly before her visit, the patient's symptoms had been aggravated. There was nothing significant in her past medical and family history.

A physical examination revealed a heliotrope rash around the eyes, poikiloderma on the left upper back(Fig. 1A) and Gottron's lesions on the metacarpal and the interphalangeal joints(Fig. 2A). Laboratory findings revealed a elevate in ESR , CPK (397.9U/L), Aldolase (10.6U/L), and LDH (189U/L), but a complete blood count, urine annalysis, VDRL, ANA, RA, LE cell, chest X-ray, EKG were within normal limits or negative. The electromyogram findings showed inflammatory myopathy, but, she refused muscle biopsy. The screening tests for associated malignancy were all unremarkable, but a pap smear was positive and the result of punch biopsy of cervix was carcinoma in situ(CIS).

A biopsy specimen from poikiloderma lesion on the left upper back showed epidermal atrophy, vacuolar alteration of basilar keratinocytes, a sparse lymphocytic inflammatory infiltrate around blood vessels, and papillary dermal melanophages(Fig. 3).

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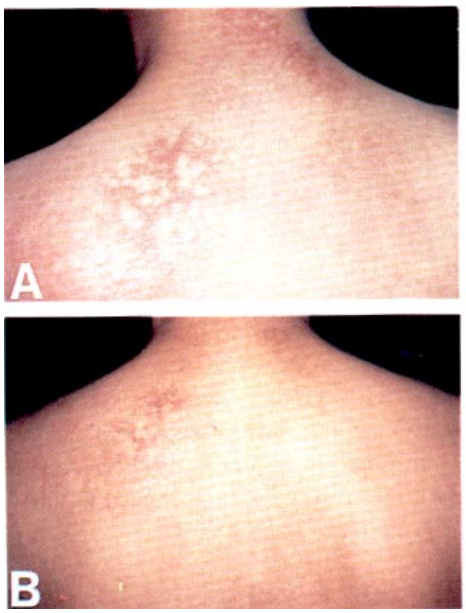

Fig. 1. (A) Poikiloderma on the left upper back and posterior neck. (B) After 10 months of treatment, the erythematous lesions of poikiloderma were improved with blotchy hyperpigmentation.

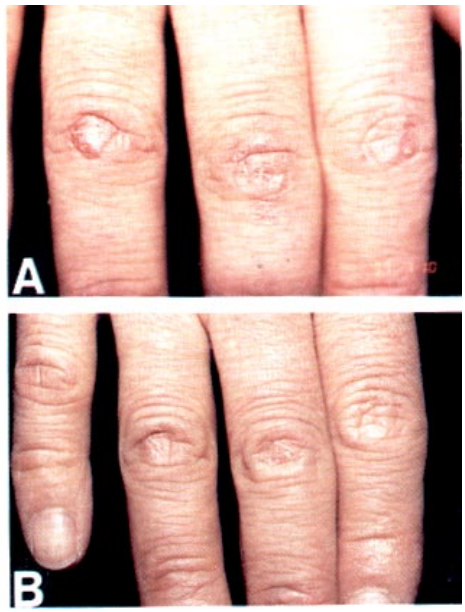

Fig. 2. (A) Gottron's papules. Erythematous papular lesions are seen over the metacarpal and distal interphalangeal joint. (B) After 10months of the treatment, Gottron's papules disappeared with some atrophy.

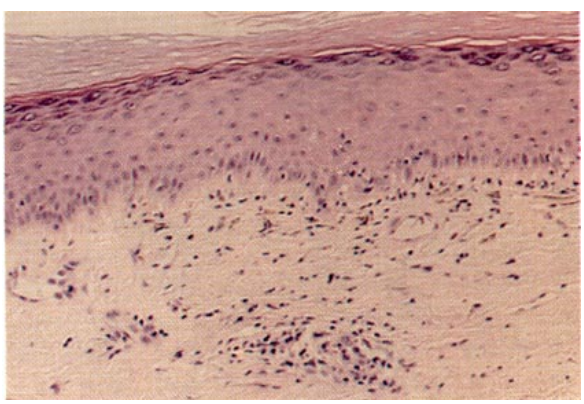

Fig. 3. An atrophic epidermis showed vacuolar alteration of basilar keratinocytes associated with a sparse lymphocytic inflammatory infiltration and papillary dermal melanophges(H&E stain, ×200).

Our therapeutic schedules and regimens are summarized in table(table. 1).

The treatments were started with a combination oral prednisolone, intramuscular methotrexate, hydroxychloroquine and the removal of cervical CIS. With therapy, the muscle enzyme (CPK and LDH) levels dropped to 124.2U/L, 118.1U/L, and muscle weakness and cutaneous lesions improved. So, we have tapered the dosages of prednisolone and methotrexate. However, two months later, her muscle enzyme levels were increased up to 289.4U/L, 187.6U/L, and muscle weakness and cutaneous lesions were aggravated. Thus we have discontinued methotrexate and hydroxychloroquine, and new combination regimens of oral prednisolone and chlorambucilwere were started. After two months of this combination therapy, her muscle enzyme levels dropped to a normal range (CPK 120.1U/L, LDH 121.3U/L), and muscle weakness and cutaneous lesions were markedly improved(Fig. 1B, 2B). At the last follow-up examination 1 year after treatment, there was no recurrence and drug-induced toxic complication.

DISCUSSION

DM is one of the idiopathic inflammatory myopathies with characteristic cutaneous findings[4]. Patients commonly present with cutaneous disease accompanied or followed shortly by proximal muscle weakness. The characteristic and possibly pathognomonic cutaneous features of dermatomyositis are the heliotrope rash and Gottron's papules. Several other cutaneous changes, include malar

Table 1. Summary of treatment regimens and results

Durations	Treatment regimens	Treatment results
First 2 months	• PDN 40mg/day + MTX 40mg IM (single) for 10days • PDN 20mg/day + MTX 20mg IM (single) for 10days • PDN 15mg/day + MTX 15mg IM (single) + Hydroxychloroquine 400 mg for 40days • Removal of cervical CIS in 20days	• CPK & LDH levels dropped. (124.2U/L & 118.1U/L) • Muscle weakness & cutaneous lesions improved
But, after first 2 months later ;	• CPK & LDH levels increased. (289.4U/L & 187.6U/L) • Muscle weakness & cutaneous lesions aggravated.	
Second 2 months	• PDN 10mg/day + Chlorambucil 4mg/day for 1 month • PDN 10mg/day + Chlorambucil 2mg/day for 1 month	• CPK & LDH levels dropped. (120.1U/L & 121.3U/L) • Muscle weakness & cutaneous lesions much improved

erythema, poikiloderma in a photosensitive distribution, and periungual and cuticular changes, occur in patients who have dermatomyositis.

The etiology and pathogenesis of DM is still unexplained[5]. Etiologically, multiple agents have been associated with the appearance of DM, including infections, postvaccination effect, drug-induced disease, stress, trauma, and neoplasm[6].

The association of DM with malignancy is controversial, but estimates of the frequency of cancer in adults with DM range from 7 to 34%[7,8]. Based upon data from case series, Callen[9] has suggested that, of the cancers association with DM, about one third occur before the myositis diagnosis, one third concurrent with diagnosis, and one third after diagnosis. The tumors may appear at any site, but the most common sites in order of frequency are the breast, lung, ovary, stomach, colon, uterus, and nasopharynx[10]. The rash and symptoms of DM may clear following resection of the tumor, and recurrence of DM may indicate the occurrence of a second primary cancer or recurrent cancer. Our case was associated with cervical CIS, and concurrently diagnosed with DM. After removal of cervical CIS, muscle weakness and cutaneous lesions were improved. However, skin and muscle symptoms were aggravated without occurrence of a second primary cancer or recurrent cancer.

Therapies for the DM are difficult to evaluate for many reasons. But, corticosteroids remain the standard therapy for DM[11,12]. Various other systemic agents have also been reported to be useful; these include prednisolone, methotrexate, antimalarials, azathioprine, cyclophosphamide, cyclosporin, chlorambucil, intravenous immunoglobulin[13-17].

Oral corticosteroids are the treatment of first choice for DM. However, up to 15-25% of adult DM patients are unresponsive to corticosteroid therapy alone or develop unacceptable steroid toxicity[17]. In these patients, alternative therapy with immunosuppre-ssive agents (methotrexate, azathioprine, cyclophosphamide, cyclosporin, chlorambucil), alone or in combination with systemic corticosteroids, has proven effective[12]. Using these immunosuppressive agents frequently enables a reduction or discontinuation of corticosteroid therapy.

The first description of effectiveness of chlorambucil on DM was that of Bohan and Peter[18] in 1977. In 1985, Wallace et al[17] reported chlorambucil in combination with prednisolone to be effective in two steroid-resistant DM patients. In 1993, Sinoway and Callen[12] reported five recalcitrant DM patients treated with oral chlorambucil. Three patients were treated with a combination of prednisolone and chlorambucil, and two with chlorambucil alone.

Chlorambucil is an alkylating agent of the nitrogen mustard type. The mechanism of action involves alkylation of nucleic acids, with resultant inhibition of DNA synthesis. The drug possesses both cytotoxic and immunosuppressive properties and is more toxic to lymphocytes than to neutrophils. Because DM is thought to result from a cell-mediated immunologic response[12], the beneficial effect of chlorambucil may be exerted through its cytotoxic

effect on lymphocytes[19]. Other dematologic uses for chlorambucil include the treatment of pyoderma gangrenosum, Behcet's disease, SLE, scleroderma, and Wegener's granulomatosis[12,19].

The most common acute side effect of chlorambucil is bone marrow suppression. It is important to closely monitor the complete blood cell count during therapy[19]. Other toxicities include sterilization, oncogenesis, hepatotoxicity, seizures, pulmonary fibrosis, drug fever[12,19].

Chlorambucil is an effective therapy for DM; both alone and in combination with corticosteroids. In particular, it should be considered for use in patients whose disease is unresponsive to high-dose corticosteroids; patients who experience coticosteroid-related toxicity; and patients who are unable to tolerate other immunosuppressive agents[11,12].

In summary, our case was successfully treated with oral prednisolone and chlorambucil. However, more experience with similar regimens be recorded.

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