Intractable Skin Necrosis and Interstitial Pneumonia in Amyopathic Dermatomyositis, Successfully Treated with Cyclosporin A

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Abstract

We report a patient with amyopathic dermatomyositis (DM) who mainly showed interstitial pneumonia and intractable skin necrosis in bilateral elbows and soles with a poor response to immunomediated therapy, including corticosteroid and high-dose intravenous immunoglobulin. Soon after starting oral cyclosporin A (CyA) the skin lesions healed completely and the interstitial pneumonia promptly improved in parallel with a decrease in serum KL-6. Since fatal interstitial pneumonia is frequently associated with amyopathic DM as in this case, administration of CyA should be actively considered as a therapeutic option when clinical symptoms are progressive and resistant to conventional treatments.


Key words: corticosteroid, high-dose intravenous immunoglobulin, KL-6

Introduction

Dermatomyositis (DM) is an inflammatory systemic disorder mainly affecting skeletal muscles and the skin, and clinically shows various eruptions mainly involving the face and dorsal portions of multiple joints in addition to muscular symptoms, including limb weakness and myalgia (1). It is well known that interstitial pneumonia is frequently associated with DM, particularly in the amyopathic form, and sometimes results in an unfavorable outcome (2). Because an autoimmune mechanism is considered to be central to the pathogenesis of the disease, corticosteroid has usually been employed as the first line of treatment to improve both muscular and skin symptoms.

Here, we describe a patient with amyopathic DM who showed interstitial pneumonia and intractable skin necrosis in bilateral elbows and soles. These symptoms were poorly responsive to intensive immunomediated therapies, including corticosteroid and high-dose intravenous immunoglobulin, but were promptly cured by the administration of cyclosporin A (CyA).

Case Report

A 24-year-old man manifested fever, arthralgia, shortness of breath and bilateral eruptions with itching in his knees, elbows and the dorsal portion of his hands in July 2001. When he was admitted to a neighboring hospital, physical examination showed slight weakness in proximal muscles in addition to the eruption. Despite lack of apparent myogenic abnormalities on electromyography (EMG), laboratory data demonstrated a slight increase in serum levels of creatine phosphokinase (CK, 272 U/l, normal value less than 250 U/l) and aldolase (7.7 U/l, normal value less than 7.5 U/l), leading to a diagnosis of probable DM according to established criteria (1). Skin biopsy from the eruption demonstrated liquefactive degeneration in the basal area of the epidermis and capillary dilatation with edema and perivascular infiltration of mononuclear cells in the dermis, mainly in the superficial zone (Fig. 1). Because of suspected active interstitial pneumonia in the bilateral lungs based on computed tomography (CT), pulmonary function tests that showed a restrictive pattern, and an increase in serum level of KL-6 (668 U/ml, normal value less than 500 U/ml), administration of oral prednisolone was started at a dose of 50 mg/day following pulse therapy with intravenous methylprednisolone (3 g...
In January 2002 eruptions reappeared in his bilateral hands, elbows and knees, and he was referred to our hospital. On physical examination he showed erythematous eruptions bilaterally on the cheek, dorsal side of small joints in the hands, knees, elbows and soles, and particularly in the last two areas skin necrosis and ulcer formations coexisted (Fig. 2A and B). Velcro rales were audible bilaterally in his lower back. Although there was no muscular weakness, he complained of difficulty in walking because of foot pain ascribable to multiple plantar ulcers. Routine laboratory data demonstrated almost normal findings, including CK (58 U/l, normal 43–272 U/l), erythrocyte sedimentation rate (7 mm/h, normal value less than 10 mm/h) and CRP (0.13 mg/dl, normal value less than 0.1 mg/dl), except for increased hepatic enzymes, including lactate dehydrogenase (337 U/l, normal 114–220 U/l), asparate aminotransferase (56 U/l, normal 12–37 U/l) and alanine aminotransferase (84 U/l, normal 7–45 U/l), ascribable to fatty liver due to long-term corticosteroid therapy. Anti-nuclear and anti-Jo-1 antibodies were negative, and KL-6 was highly elevated in serum (1,890 U/ml). No anti-neutrophil cytoplasmic antibodies (ANCA) specific for either myeloperoxidase or proteinase-3 could be detected in serum. CT showed reticulonodular shadows without apparent honeycombing in the bilateral lungs, but predominantly on the left (Fig. 3A and B), coinciding with the positive shadow on 67Ga-scintigraphy. In pulmonary function tests diffusion capacity rate of the lung for carbon monoxide (%DLCO) was decreased to 63.2% though other parameters, including vital capacity (%VC), were normal. Despite intensive systemic surveys there were no abnormal findings suggestive of malignancy.

Although oral prednisolone was increased to 60 mg/day soon after admission, the patient’s cutaneous lesions gradually worsened, particularly in the bilateral elbows and soles, and serum KL-6 rose to around 3,000 U/l in early February (Fig. 4). After high-dose intravenous immunoglobulin therapy (IVIg) performed twice at 0.4 g/kg/day for 5 days with an interval of around one month, in addition to oral prednisolone, the skin lesions in the bilateral hands and soles were slightly improved, but those on elbows worsened further. Despite a slight decrease in the serum level of KL-6 the interstitial pneumonia also worsened on CT, and pulmonary function tests showed a %DLCO of 49.7%. In early April, therefore, oral CyA was started at a dose of 150 mg/day, and the plasma concentration was kept to 100–150 ng/ml at the trough level. Skin necrosis in the bilateral elbows and soles soon improved, and the patient found no difficulty in walking. In parallel with a decrease in the serum level of KL-6 the interstitial pneumonia improved on both physical examination and CT (Fig. 3C and D). In early May 2002 the ulcers in the bilateral elbows and soles had completely healed (Fig. 2C and D), and he left our hospital in the middle of June. In the outpatient clinic oral prednisolone has since been tapered to 10 mg/day, and he has shown no exacerbation in either skin lesions or interstitial pneumonia with KL-6 at a level of 700–900 U/l.

Discussion

Biopsy from cutaneous lesions demonstrated the typical histopathology for DM, and this patient fulfilled the diagnostic criteria for probable DM at the previous hospital (1). In this patient, however, muscular symptoms ascribed to DM transiently developed with a slight elevation in the serum level of CK only in the early phase of illness, and the main symptoms were cutaneous manifestations and interstitial pneumonia throughout the clinical course, particularly after admission to our hospital. These features largely meet the general criteria for amyopathic DM, which has recently become accepted as a clinical entity. According to the original description, this disease is characterized by eruptions typical of DM and no muscular involvement (3). However, precise diagnostic criteria have not yet been established, and there have been several case reports that do not conform to the original definition (2, 4–6). To make a diagnosis of amyopathic DM, at least the following two clinical features are necessary: eruptions typical of DM and no or little muscular involvement with some evidence suggesting the presence of myositis (6). In these respects this patient was...
considered to have amyopathic DM from the onset of illness. In general, corticosteroid is effective for muscular and skin symptoms in more than 50% of patients with DM (7, 8), but this patient showed a poor response to this drug especially for the cutaneous lesions. When patients with DM are resistant to corticosteroid treatment, the next therapeutic option is usually immunosuppressive agents, including azathioprine, cyclophosphamide and methotrexate (9). The former two, however, show toxic effects on reproductive function as well as being carcinogenic, and informed consent could not be obtained from our young male patient. Methotrexate was considered to be very risky because of its potential to worsen the interstitial pneumonia. Recently, IVIg has been shown to have good therapeutic effects on muscular symptoms ascribed to DM in several reports (8, 10, 11), and immunological modulation of various pathological processes is considered to be relevant to the efficacy of this therapy (12). In this patient, the skin necrosis in the hands and soles

Figure 2. Photographs of bilateral soles and the left elbow, showing skin necrosis with ulcer formation on admission to our hospital (A, B) and complete recovery at discharge after starting cyclosporin A (C, D).
seemed to improve slightly after IVIg, but the therapeutic effects were insufficient for the ulcers on the elbows and the interstitial pneumonia. In addition, intractable DM sometimes requires additional administration of IVIg to prolong the therapeutic effects and avoid a relapse of muscular and skin manifestations (8, 11). Considering the extremely high cost of IVIg, a different treatment was inevitably selected in this patient.

Another candidate drug for DM, CyA, has recently been employed in intractable cases in several reports, and has shown good therapeutic effects for both muscular and skin symptoms (7, 13–18). Saadeh et al reported two patients with DM refractory to corticosteroid therapy who were successfully treated with CyA in combination with IVIg (7). CyA is classified among the immunosuppressive agents acting as calcineurin inhibitors, and reversibly and strongly suppresses cytokine production mainly from helper T cells (19). With regard to adverse effects important in young patients, as in this case, including alopecia and toxicity for reproductive function, CyA is superior to other immunosuppressive agents such as azathioprine and cyclophosphamide, though monitoring of the serum trough concentration is always necessary to avoid nephrotoxicity (20, 21). Another advantage of CyA is that therapeutic effects appear within 1 to 2 weeks, whereas other immunosuppressive agents usually require at least 2 to 3 months (13–15). In this patient, therefore, we tried CyA following IVIg with his informed consent. Soon after starting CyA the skin necrosis showed a reduction in size, particularly in both elbows, and completely healed within around one month.

In amyopathic DM, intractable interstitial pneumonia occasionally develops, as in this patient, and sometimes leads to death (2). When this complication is poorly responsive to corticosteroid alone, immunosuppressive agents such as cyclophosphamide have often been employed as an additional therapy (22). Nevertheless, the results are not always satisfactory (22), and therapeutic efficacy for this complication has never been confirmed also with other immunomodulatory treatments, including IVIg. According to several recent reports CyA has also been employed for this intrac-
Successful Treatment of DM with CyA

Table 1: Clinical course of the patient. %DLCO: diffusion capacity rate of the lung for carbon monoxide, SpO2: percutaneous oxygen saturation, IVIg: high-dose intravenous immunoglobulin.

Figure 4. Clinical course of the patient. %DLCO: diffusion capacity rate of the lung for carbon monoxide, SpO2: percutaneous oxygen saturation, IVIg: high-dose intravenous immunoglobulin.

In conclusion, CyA might be a key drug in the treatment of amyopathic DM. When patients with this disease show intractable skin necrosis and interstitial pneumonia, CyA therapy should be actively considered as early as possible.

References
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