High-Dose Immunoglobulin Therapy for a Patient with Dermatomyositis

Yukiko Furuya, Toru Takahashi, Hirohide Hamamoto, Masaharu Nishimura and Yoshikazu Kawakami

A 46-year-old woman was admitted to our department complaining of dermal eruption and weakness of muscles. She was diagnosed as having dermatomyositis and was initially treated with prednisolone. Since her condition rapidly deteriorated, high-dose intravenous immunoglobulin (IVIG) therapy (0.4 g/kg/day i.v. for 5 days) was administered. Marked improvement in muscle strength was observed the following day after the first administration. She unfortunately died of pneumocystis carinii pneumonitis 2 weeks after the IVIG therapy. Autopsy revealed no inflammatory cells in the muscles, suggesting that IVIG therapy has an important clinical application for refractory dermatomyositis.

Key words: intravenous immunoglobulin (IVIG), refractory myositis, pneumocystis carinii, corticosteroid resistant

Introduction

Dermatomyositis (DM) is an inflammatory muscular disease of unknown etiology. Since immunological mechanisms are thought to contribute to muscle and connective tissue injury, the first line therapy is administration of corticosteroids alone and/or immunosuppressive drugs such as azathioprine, methotrexate, cyclosporine or cyclophosphamide. However, not all patients with DM necessarily benefit from these medications. Recently, high-dose intravenous immunoglobulin (IVIG) therapy has received considerable attention for refractory DM (1-5).

Here, we report a patient with refractory DM who showed a dramatic response to high-dose IVIG therapy.

Case Report

A 46-year-old Japanese woman had been well until she first noticed a palm eruption in April 1994. Then, slight fever, polyarthralgias, arthral swelling and muscle weakness in bilateral upper and lower limbs appeared. The skin eruptions spread rapidly across the whole body. She began to feel difficulty in standing up and was admitted to our department on May 17. Her past medical history was unremarkable and she had no family history of neuromuscular diseases. Physical examination on admission showed height of 159 cm, body weight of 56 kg, and body temperature of 37.6°C. In both lower lobes, there were fine crackles in lung auscultation. The color of her fingernails was black and the skin rash, which appeared on the forehead, neck and shoulders, chest and back, forearms and lower legs, was dusky and erythematous. Periorbital edema with heliotrope hue was also detectable. She had erythematous plaques over the knuckles of the fingers (Gottron’s sign). Neurologic examination confirmed proximal muscle weakness of grade 4/5 power involving the shoulder, hip girdles and elbows in a symmetrical distribution. Laboratory data revealed elevation of muscle specific enzymes as follows; creatine kinase (CK) 216 IU/l (100% of MM form isozyme), serum aldolase 10.7 IU/l, aspartate aminotransferase (AST) 200 IU/l, alanine aminotransferase (ALT) 128 IU/l, lactic acid dehydrogenase (LDH) 819 IU/l. Auto antibodies including anti-nuclear antibody, anti-DNA antibody, and anti-Jo1 antibody were all negative. Pulmonary function tests including vital capacity, forced expiratory volume in one second, and diffusing capacity were within normal limits, but arterial blood gas analysis revealed slight hypoxemia (partial pressure of oxygen (PaO₂) 74.0 Torr) with normal pH (7.43) and partial pressure of carbon dioxide (PaCO₂) (40.9 Torr). Chest roentgenogram (Fig. 1) and chest computed tomography (CT) scan revealed focal ground-glass opacities in both lower lobes without honey-comb formation. Electromyography of the quadriceps femoris showed a myopathic pattern with abnormally brief action potentials of low amplitude and
fibrillation potentials. Gastroendoscopy and abdominal CT scan revealed no evidence of malignancy. We performed muscle biopsy on the quadriceps femoris, but failed to get enough volume of muscle tissue for pathological diagnosis.

She was clinically diagnosed as having DM, based on proximal muscle weakness, characteristic skin rash, elevated muscle enzymes in serum and characteristic electromyographic abnormalities. She was initially treated with oral prednisolone at a dose of 1 mg/kg/day, but her general condition worsened. Although high-dose corticosteroid pulse treatment at a dose of 1 g/day over three days was additionally attempted, the weakness and tenderness of her muscles did not improve and serum CK activity increased further up to 3,735 U/l (Fig. 2). She began to complain of dysphagia, dysphonia, muscle pain and swelling of the chest muscles and the right upper arm. She finally could not raise her head up from the pillow. She was diagnosed as having disseminated intravascular coagulation (DIC) syndrome because of skin bleeding, thrombocytopenia, a reduced fibrinogen level, and elevated levels of fibrinogen degradation products. Rapid deterioration of her condition prompted us to determine use of high-dose IVIG at a dosage of 0.4 g/kg/day over five days. The next day after the first administration of high-dose IVIG, her skin lesions and muscle strength improved. Dysphagia, dysphonia and swelling of the chest muscles disappeared and she could turn in bed. Concomitantly with the improvement of the skin lesions and muscle strength, the levels of serum CK activity gradually declined and returned to a normal range after two weeks. However, she suddenly complained of dyspnea and arterial blood gas analysis revealed severe hypoxemia (PaO₂ 52 Torr) two weeks after the IVIG therapy. Intriguingly, there was no evidence of aberrant auscultation in the lungs except for fine crackles in both lower lung areas. Diffuse, bilateral infiltrations were seen on the chest roentgenogram. Pneumocystis carinii was identified in cytological examinations of bronchial lavage and chemotherapy (Trimethoprim-sulfamethoxazole and pentamidine) was initiated. Her hypoxemia progressed and she had to be put on a ventilator. She died of respiratory failure on July 17. Her clinical course is summarized in Fig. 2.

Autopsy revealed focal degeneration of the skeletal muscles...
without any infiltration of inflammatory cells (Fig. 3) and with some calcification. Pulmonary examinations showed bilateral atherectomy with clear yellowish effusion. Histologically, marked infiltration of inflammatory cells and focal organization were observed in the alveolus. Alveolar septum was noted as having slight fibrotic change and mild degradation. Although pneumocystis carinii was not detected in grocott staining, it was compatible with pneumocystis carinii pneumonia.

**Discussion**

DM is characterized by an intramuscular microangiopathy mediated by the complement C5b-9 membranolytic attack complex, leading to loss of capillaries, muscle ischemia, muscle-fiber necrosis, and perifascicular atrophy. Recently high-dose IVIG therapy has been noted for its use for refractory DM (5).

Roifman et al first reported a trial of IVIG therapy for the treatment of inflammatory myopathies in 1987 (1). Subsequently, several uncontrolled studies appeared which demonstrated the effectiveness of IVIG therapy for polymyositis (PM) and DM (2–4). In 1993, the first double-blind, placebo-controlled study was reported from the National Institute of Health (NIH) which concluded that high-dose IVIG therapy was a safe and effective treatment for refractory DM (5). High-dose IVIG therapy has been successfully used also for some other immune-related neuromuscular disorders (6–11). However, the mechanisms by which this treatment is effective for patients with DM remain unclear, although there are several proposed mechanisms. One of the findings related to the pathogenesis of DM is that immune globulin blocks Fc receptors on the vascular walls. IVIG therapy may prevent the attachment of immune complexes through competition for the Fc receptors of blood vessels (12, 13). Secondly, IVIG therapy may inhibit the effects of activated T cells, released cytokines, and lymphokines (12, 13), or their competition with MHC molecules (14, 15). Thirdly, IVIG may neutralize complement neoantigens (16) and inhibit the formation of the membranolytic attack complex from the activated C4b and C3b fragments (17), thereby preventing its subsequent binding to target cells. So far there have only been a few documents which recognized adverse side effects associated with high-dose IVIG therapy. Reported side effects include headaches, decline in blood pressure, heart failure, delirium and infection (2, 6, 18, 19), some of which may not be related to the pharmacological reaction, but rather to the method of injection.

In the present case, the patient’s condition became progressively worse with complicated DIC syndrome which may be attributed to the aggravation of DM, but her condition dramatically improved after IVIG therapy. Although we cannot completely deny the possible effect of the steroid therapy, we assumed that her dramatic improvement was due to IVIG therapy in view of her clinical course. Her condition demonstrated that the apparent effect of IVIG therapy appeared immediately after the therapy was administered. Skin lesions cleared the day after the first administration of IVIG. The serum CK level also dropped immediately and decreased to a normal range within two weeks. The autopsy findings revealed no inflammatory cells accumulated in muscles, which further supports the efficacy of this therapy. The findings of focal degeneration and several calcifications in skeletal muscles might also be evidence of the improvement.

In summary, we report a case in which a high-dose IVIG therapy was dramatically effective for steroid-resistant DM. Autopsy revealed no inflammatory cells in the muscles, suggesting that IVIG therapy has an important clinical application for refractory dermatomyositis.

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**References**

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789, 1993 (see comments).


