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Case Report

High-dose intravenous immunoglobulin therapy for rapidly progressive interstitial pneumonitis accompanied by anti-melanoma differentiation-associated gene 5 antibody-positive amyopathic dermatomyositis

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Abstract

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive amyopathic dermatomyositis (ADM) associated with rapidly progressive interstitial pneumonitis (RPIP) frequently has a poor prognosis and optimal treatment is not well defined. Here, we report a 62-year-old Japanese man with anti-MDA5 antibody-positive ADM associated with RPIP presented with progressive shortness of breath, Heliotrope rash, Gottron's papules, arthralgia, and fatigue but no sign of muscle weakness. Laboratory investigation revealed serum levels of the following biomarkers: ferritin, 1393 ng/mL; Krebs von der Lungen-6, 1880 U/mL; and creatine kinase, 85 U/L. Computed tomography (CT) images showed diffuse ground-glass opacity in both lung fields. Because anti-MDA5 was positive, we made a diagnosis of ADM associated with RPIP and initiated treatment. Following five courses of combination therapy with prednisolone, cyclosporine A, and intravenous cyclophosphamide (IVCY), IVCY treatment was switched to high-dose intravenous immunoglobulin therapy (IVIg) because of the reactivation of interstitial pneumonia with an increased serum ferritin level. Additional treatment with IVIg improved RPIP, with normalization of anti-ADM antibody levels. Therefore, IVIg mayt be a new candidate treatment for anti-MDA5 antibody-positive ADM associated with RPIP.

Keywords: Amyopathic, dermatomyositis, interstitial pneumonitis, anti-MDA5 antibody

Introduction

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is a serological marker for dermatomyositis (DM) (1). Anti-MDA5 antibody is closely related to rapidly progressive interstitial pneumonitis (RPIP) associated with amyopathic dermatomyositis (ADM), particularly in Asian populations. RPIP secondary to ADM can be resistant to aggressive therapy and sometimes even fatal (2). Here, we report a case of anti-MDA5 antibody-positive ADM associated with RPIP and discuss high-dose intravenous immunoglobulin (IVIg) therapy as a possible therapeutic agent.

Case Presentation

A 62-year-old Japanese man was admitted to our hospital with shortness of breath, Heliotrope rash, Gottron's papules, arthralgia, and fatigue. He had no signs of muscle weakness and myalgia. Laboratory investigation revealed serum levels of the following biomarkers: lactate dehydrogenase, 400 IU/L (119-229 IU/L); Krebs von der Lungen-6 (KL-6), 1880 U/mL (105-435 U/mL); creatine kinase, 85 U/L (62-287 U/L); and ferritin, 1393 ng/mL (39.9-465 ng/mL) (Table 1). Cytopenia, indicative of hemophagocytic syndrome, was not revealed. The serum level of anti-MDA5 antibody was 202.929 (<8). High-resolution computed tomography (HRCT) of chest scans showed diffuse ground-glass opacities (GGOs) from the upper to lower lung fields (Figure 1a-c). Magnetic resonance imaging showed no evidence of myositis. Therefore, the patient was diagnosed with ADM-associated RPIP. We initiated combination therapy with oral prednisolone (PSL) (Prednisolone, Shionogi & Co, Japan) (50 mg/day), cyclosporine A (CyA) (Neoral, Novartis) (100 mg/day), and intravenous cyclophosphamide (IVCY) (Endoxan, Shionogi & Co, Japan) (600 mg/body/2 weeks). The ideal peak level of CyA was 1000 ng/mL. In addition, polymyxin-B direct hemoperfusion (PMX-DHP) treatment as an extracorporeal blood filter was conducted for 2 days. After five courses of IVCY, treatment was switched to high-dose IVIg (Venoglobulin, Japan Blood Products Organization, Japan) (0.4 g/kg/day for 5 days), resulting in the combination therapy with PSL, CyA, and IVIg because of both pancytopenia and the development of hypoxemia due to the recurrence of interstitial pneumonitis (IP) with increased se-

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Table 1. Changes in clinical data over the course of treatment

Clinical data	Reference range	Day 1 (admission)	Day 15 (after PSL, CyA, IVCY, and PMX-DHP)	Day 92 (IVCY switched to high-dose IVIg)	Day 326 (discharge)
P/F ratio		481	418	480	380
LDH (IU/L)	<229	400	208	317	205
KL-6 (U/mL)	<435	1880	1452	1902	314
Ferritin (ng/mL)	<465	1393	1970	2599	296
Anti-MDA5 Ab (units)	<8	202.929			3.474

LDH: lactate dehydrogenase; KL-6: Krebs von der Lungen-6; MDA5 Ab: melanoma differentiation-associated gene 5 antibody; PSL: prednisolone; CyA: cyclosporine A; IVCY: intravenous cyclophosphamide; PMX-DHP: polymyxin-B direct hemoperfusion; IVIg: intravenous immunoglobulin

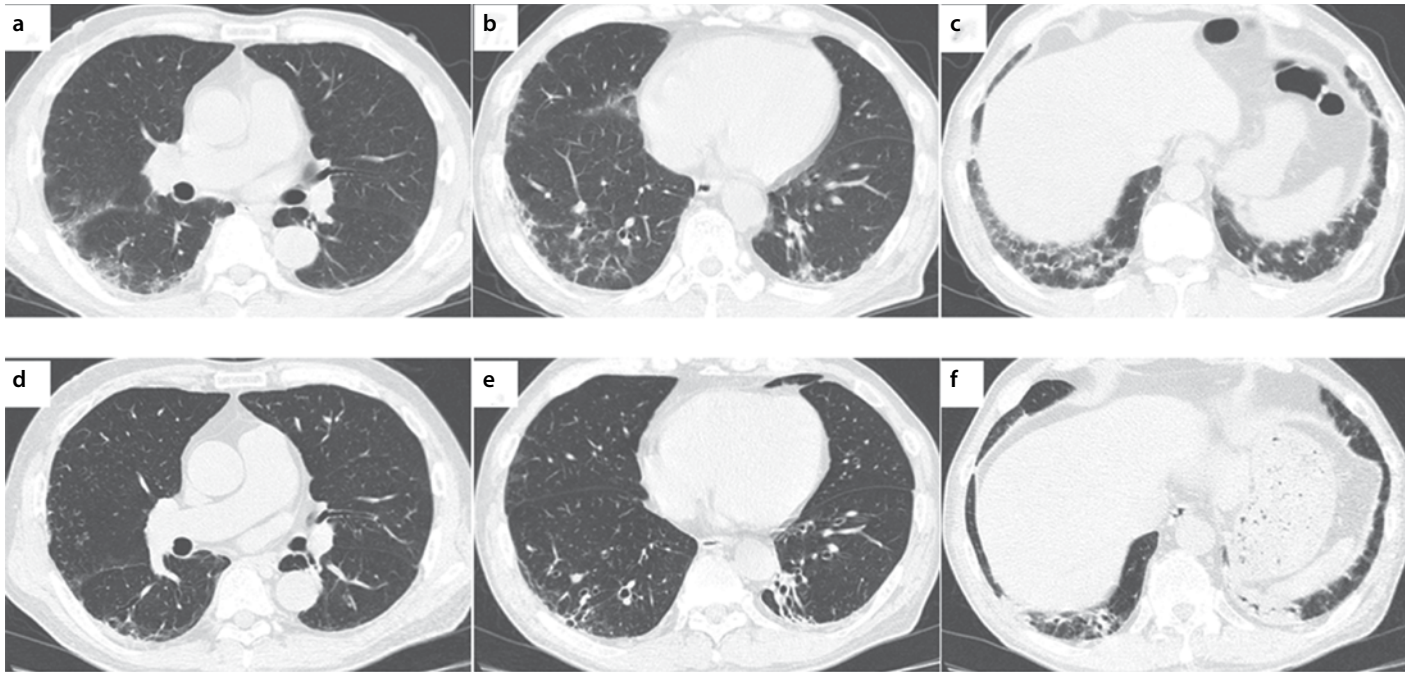

Figure 1. a-f. Diffuse ground-glass opacity was apparent in both lung fields (a-c) in CT images of the patient's lung. The reduction of ground-glass opacity after combination treatment was revealed (d-f)

rum ferritin level (peak: 2599 ng/mL) (Table 1). Pancytopenia, indicating drug-induced cytopenia, was improved by the discontinuation of IVCY. Additional treatment with IVIg improved ADM associated with RPIP (ferritin: 296 ng/mL, KL-6: 314 U/mL) and reduced GGOs (Figure 1d-f). Eleven months after admission, the patient was discharged under daily maintenance therapy with oral PSL 11 mg and CyA 100 mg. Anti-MDA5 antibody level was reduced (3.474 units), with no clinical flare-up (Table 1).

Discussion

This study demonstrated the success of combination therapy with PSL, CyA, IVCY, and PMX-DHP, followed by high-dose IVIg for the treatment of anti-MDA5 antibody-positive ADM associated with RPIP. Gono et al. (2) reported that a high ferritin level on admission was a poor prognostic factor in RPIP patients with DM, including anti-MDA5 antibody ADM. Regarding autoimmune disorders, the highest ferritin levels have been reported in patients with macrophage activation syndrome. Gono et al. (3) suggested that in patients with DM, hyperferritinemia indicated over-activation of alveolar macrophages and caused fatal injury to the lungs.

Concerning the treatment for DM associated with fatal lung injury, Dalakas et al. (4) reported that calcineurin inhibitors could promote early recovery and reduce mortality. CyA strongly suppresses cytokine production, particularly from helper T cells. Kameda et al. (5) reported that combination therapy with PSL, CyA, and IVCY improves the survival rate in DM associated with acute or subacute IP. Early intervention with CyA in combination with corticosteroid was also effective (6). In the present case, however, the effect of this early intervention was only temporary. Gono et al. (3) reported a cumulative 6-month survival rate of only 62.7% for 19 DM patients with acute/subacute IP (A/SIP) [PSL alone (n=3), PSL + CyA (n=7), PSL+IVCY (n=5), and PSL + CyA (n=4) or tacrolimus+IVCY (n=4)]. However, a proportion of these patients with A/SIP died despite combination therapy, which was possibly due to the presence of hyperferritinemia. Gono et al. (3) reported that survival in patients with DM with A/SIP differed between patients with low and high (>1500 ng/mL) baseline ferritin levels, with the latter having a bad prognosis. Moreover, a previous report suggested that complexes of the MDA5 and the anti-MDA5 antibody play a significant role in lung tissue injury (7), and a recent report suggested that anti-MDA5 antibody is nearly undetectable in survivors of ADM associated with RPIP (7). In the present case, however, anti-MDA5 antibody could not be detected when IVCY was switched to high-dose IVIg. Therefore, we consider that anti-MDA5 antibody associated with hyperferritinemia may highlight the need for additional new treatment in, particularly Asian, patients with DM.

IVIg is an important treatment for patients with refractory PM/DM and is effective in the major-

ity of PM/DM patients with lung and esophageal involvement (8). Cherin et al. (9) evaluated the long-term efficacy of combination therapy with corticosteroid and IVIg in patients with PM/DM, including those with refractory or relapsed disease. The mechanism by which IVIg improves refractory PM/DM has not been fully elucidated. Quick A et al. (10) reported that in PM/DM, IVIg diminishes the activity of complement and deposition of membrane attack complex on capillaries and muscle fibers as well as the expression of adhesion molecules and cytokine production. IVIg may also suppress T-cell activation, prevent T-cell migration into muscle tissue, and alter cytokine production (10). The relative safety of IVIg is also an important advantage. Our patient was treated with aggressive therapy from the beginning of admission and was severely immunocompromised. Because there was a high possibility of developing a serious infection, IVIg was safer than other immunosuppressive drugs.

In conclusion, this case suggests that high-dose IVIg is a novel therapeutic agent for patients with refractory ADM associated with RPIP.

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Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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