



Early intervention of plasma exchange combined with intensive immunosuppressive treatment for anti-MDA-5 antibody-positive rapidly progressive interstitial pneumonia: Two case reports

Mayuko Ishiwari^{*}, Yuki Togashi, Hiroyuki Takoi, Ryota Kikuchi, Junichiro Kawagoe, Kazutoshi Toriyama, Akane Tanaka, Yoko Nagotomo, Hayato Kinoshita, Yuta Kono, Shinji Abe

Department of Respiratory Medicine, Tokyo Medical University Hospital, Tokyo, Japan

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ABSTRACT

Background: Anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab) has to be reported to often cause rapidly progressive interstitial lung disease (RP-ILD) especially in East Asian countries. Even with the recommended rapid administration of immunosuppressive agents with high-dose corticosteroids, intravenous pulse cyclophosphamide, and calcineurin inhibitors, the prognosis of anti-MDA5 Ab-related RP-ILD is poor. Plasma exchange (PE) has been reported to be effective for steroid-refractory RP-ILD with anti-MDA5 Ab. However, the timing, frequency, and interval of PE for the treatment of RP-ILD with anti-MDA5 Ab have not yet been established.

Case presentation: We report two cases of RP-ILD with anti-MDA5 Ab treated by early intervention of PE combined with immunosuppressive treatment. Blood biomarkers including titers of anti-MDA5 Ab, serum KL-6 and ferritin were promptly decreased after each session of PE. Clinical symptoms, oxygenation and chest computed tomography abnormalities were completely improved after immunosuppressive treatment with PE.

Conclusion: Early intervention of PE combined with immunosuppressive treatment may prevent the development to lethal severe respiratory failure in RP-ILD with anti-MDA5 Ab.

1. Introduction

Anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab) is closely associated with rapidly progressive interstitial lung disease (RP-ILD). The survival rate of anti-MDA5 Ab-positive patients with interstitial pneumonia has been reported to be low in East Asian countries [1,2]. Although the rapid administration of immunosuppressive agents with high-dose corticosteroids, intravenous pulse cyclophosphamide (IVCY) and calcineurin inhibitors is recommended immediately after the diagnosis of interstitial pneumonia with anti-MDA5 Ab, hospital mortality rates in intensive care units exceeding 80% have been reported [3]. It seems to be crucial to prevent the development of respiratory failure in interstitial pneumonia with anti-MDA5 Ab. Plasma exchange (PE) is a therapeutic procedure used to treat a variety of diseases that involves the bulk removal of pathogenic substances, such as pathogenic antibodies, immune complexes, and cytokines with enhanced macrophage/monocyte function [4]. Recent reports suggest that PE is effective for steroid-refractory interstitial

pneumonia associated with anti-MDA5 Ab [5–7]. However, the indication criteria, timing, and interval for PE in RP-ILD with anti-MDA5 Ab have not yet been established. Herein, we report two cases of RP-ILD associated with anti-MDA5 Ab treated with early intervention of PE combined with intensive immunosuppressive treatment. Clinical symptoms including oxygenation, skin lesions, chest CT interstitial abnormalities and serum biomarkers were promptly improved after PE concomitant with intensive immunosuppressive treatment.

2. Case presentation

2.1. Case 1

A healthy 66-year-old Japanese woman was admitted to the hospital with a 2-week history of progressive shortness of breath. She reported having muscle pain in both thighs for 3 months before hospital admission. She had no history of smoking and no family history of autoimmune disorders. Physical examination revealed fine crackles in both

^{*} Corresponding author. Department of Respiratory Medicine, Tokyo Medical University Hospital, 6Nishi-Shinjuku, Shinjuku-ku, Tokyo, 160Japan, E-mail address: mayuko@tokyo-med.ac.jp (M. Ishiwari).

lower lungs, Gottron's sign, heliotrope rash, and periungual erythema of the skin without muscle weakness. On admission, her oxygen saturation (SpO₂) was 95% on room air. Arterial blood gases revealed a PaO₂ of 68.7 mmHg, PaCO₂ of 33.2 mmHg and AaDO₂ 39.8 Torr. Laboratory findings were as follows: white blood cell count, 4500/μL (neutrophils, 68.8%; lymphocytes, 22.4%; monocytes, 0.3%; eosinophils 1.1%; basophils, 0.4%); hemoglobin, 13.0 g/dL; platelet count, 224,000/μL; C-reactive protein, 1.25 mg/dL; aspartate aminotransferase, 39 IU/L; alanine aminotransferase, 16 IU/L; alkaline phosphatase, 244 IU/L; γ-glutamyl transpeptidase, 24 IU/L; CK, 200 IU/L (reference range, 43–165 IU/L); Krebs von den Lungen (KL)-6, 833 U/mL (reference range, 105.3–401 U/mL); ferritin, 611.8 ng/ml (reference range, 6–138 ng/ml); and anti-MDA5 Ab, 1350 index (reference values, <32 index). Anti-MDA5 autoantibody was commercially measured by enzyme-linked immunosorbent assay (ELISA) kit (SRL). High-resolution computed tomography (HRCT) chest examination showed patchy consolidation and ground-glass opacity (GGO) in the lower lobes of both lungs (Fig. 1A). Transbronchial lung biopsy from left lower lobe revealed alveolar septal fibrosis and moderate inflammation with lymphocyte infiltration consistent with anti-MDA5 Ab associated interstitial pneumonia. She was diagnosed as RP-ILD with anti-MDA5 Ab-positive dermatomyositis. On day 1, high-dose corticosteroid (methylprednisolone 1g/day for 3 days) was started with oral tacrolimus (trough concentration 5–10 ng/ml) and intravenous cyclophosphamide (IVCY, 800 mg/day). However, her clinical symptoms including shortness of breath and skin eruption worsened, and her serum ferritin level increased to 1200 ng/ml. The pulse oximetric saturation (SpO₂)/FiO₂ (S/F) ratio was declined from 452 to 342 one week after the initial immunosuppressive treatment. In order to prevent the progression to severe respiratory failure due to hyperinflammation state, the first session of PE was started three times per week. PE was performed using 5%

albumin as the main replacement fluid. Fresh frozen plasma was administered at the end of the session to prevent coagulopathy. The plasma volume exchanged during the session was 5000 ml. After the first PE session, serum levels of anti-MDA5 Ab and ferritin decreased to 102 units and 586 ng/ml, respectively (Fig. 2). The S/F ratio improved to 457 after the 1st session of PE.

Although triple therapy (prednisolone followed by 1 mg/kg tapering, tacrolimus and IVCY) was continued after the first PE session, her ferritin and anti-MDA5 Ab serum levels increased once more and Gottron's sign worsened again about 3 weeks post 1st PE. On day 34, the second PE session was carried out following the same procedure as the first PE. Serum levels of anti-MDA5 Ab, KL6, and ferritin decreased to the normal range after 2nd session of PE (Fig. 3) and the bilateral consolidation and GGO on chest HRCT subsequently improved (Fig. 1B). Thereafter clinical symptoms have been maintained stable and blood markers including anti-MDA5 Ab, KL-6 and ferritin have been kept to be within the normal range. Remission has been maintained for more than 1 year with low dose prednisolone and tacrolimus.

2.2. Case 2

A healthy 42-year-old Japanese woman was admitted to the hospital with a 1-month history of rapidly progressive shortness of breath. Physical examination revealed typical skin changes, such as Gottron's sign, inverse Gottron's sign, and the V-sign, as well as scratch dermatitis on her back. Chest HRCT revealed bilateral consolidations and GGO consistent with interstitial pneumonia due to dermatomyositis (Fig. 1C). On admission, her oxygen saturation (SpO₂) was 98% on room air. Arterial blood gases demonstrated a PaO₂ of 85.1 mmHg and PaCO₂ of 34.2 mmHg. An oxygen supplement with 1 L/min via a nasal cannula was started because her SpO₂ was decreased to 88% when walking on

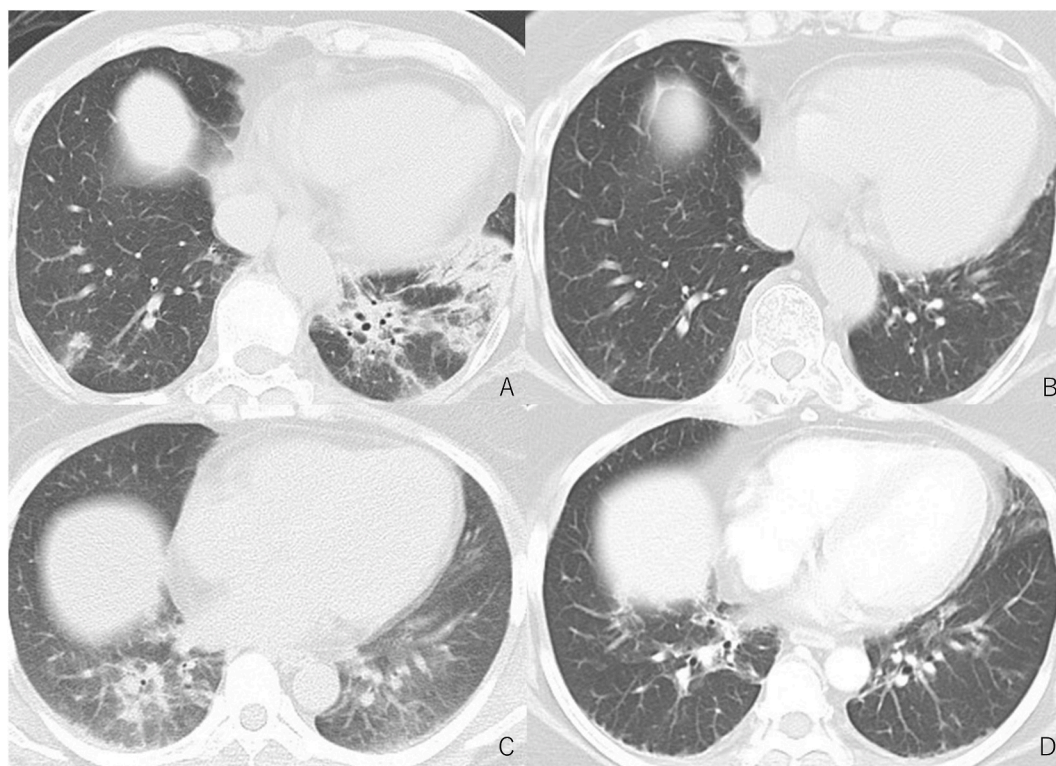


Fig. 1. Chest CT images in case 1 (A, B) and case 2 (C, D)

A, Chest CT images in case 1 at admission showed patchy consolidation, ground-glass opacities (GGO) and traction bronchiectasis predominantly in bilateral lower lobes. B, Chest CT images in case

1 showed improvement of consolidation and GGO after two sessions plasma exchange (PE) with intensive immunosuppressive treatment compared to those of admission. C, Chest CT images in case 2 at admission showed bilateral consolidations and GGO in bilateral lower lobes. D, Chest CT images in case 2 after 1st session of PE showed improvement of both consolidation and GGO compared to those of admission.

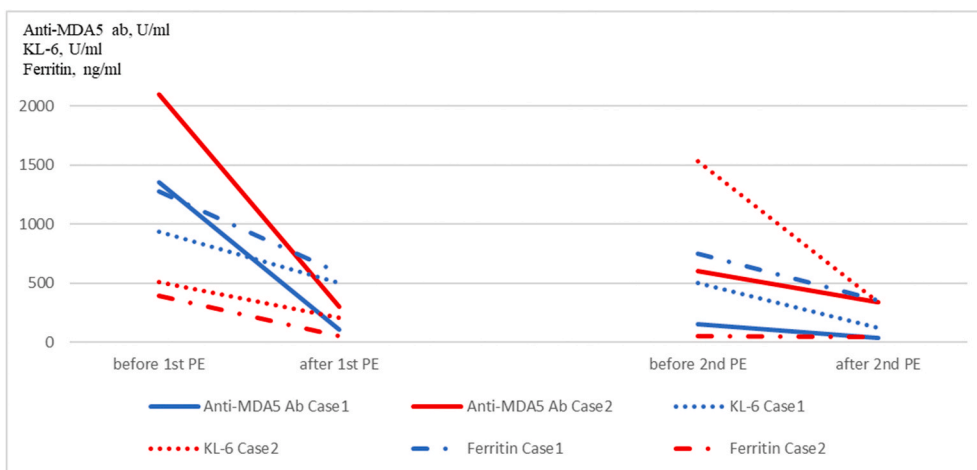


Fig. 2. Improvement in titers of anti-MDA5 Ab and serum KL-6 and ferritin values after PE. Clinical parameters (serum titers of anti-MDA5 Ab, KL-6 and ferritin) for RP-ILD with anti-MDA5 Ab were promptly decreased after both 1st and 2nd session of PE.

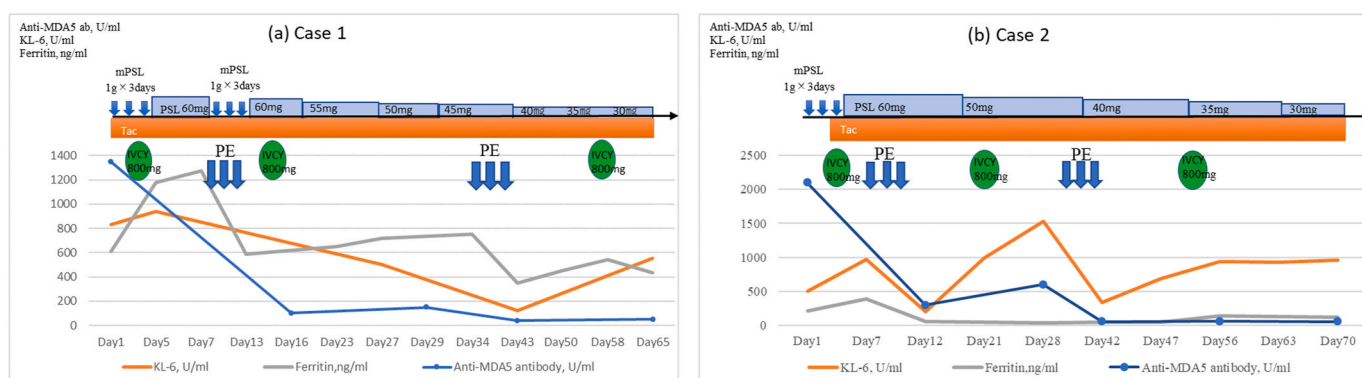


Fig. 3. Clinical course and changes in parameters of Case 1 (a) and Case 2 (b)

Serum titers of anti-MDA5 Ab, KL-6 and ferritin, and the therapeutic interventions were shown. After 2 sessions of PE, blood parameters were maintained to be stable as well as improvement clinical symptoms.

room air. Laboratory findings were as follows: white blood cell count, 6000/ μ L (neutrophils, 85.3%; lymphocytes, 7.0%; monocytes, 6.4%; eosinophils 1.2%; basophils, 0.1%); hemoglobin, 9.4 g/dL; platelet count, 327,000/ μ L; C-reactive protein, 3.38 mg/dL; aspartate aminotransferase, 26 IU/L; alanine aminotransferase, 13 IU/L; alkaline phosphatase, 45 IU/L; γ -glutamyl transpeptidase, 21 IU/L; CK, 200 IU/L (reference range, 43–165 IU/L); aldolase (ALD), 4.7 IU/L (reference range, 2.1–6.1 IU/L); KL-6, 506 U/mL; and soluble interleukin-2 receptor, 970 IU/L (reference range, 122–496 IU/ml); ferritin, 209 ng/ml (reference range, 6–138 ng/ml); anti-MDA5 Ab, 2100 index; IL-6, 36.3 pg/ml (reference range, 4.0 >pg/ml), IL-8, 55.4 pg/ml (reference range, 2.0 >pg/ml); IL-18, 854 pg/ml (reference range, 126 \pm 44.5 pg/ml).

Magnetic resonance imaging revealed extensive T2 short-tau inversion recovery (STIR)-hyperintense lesions and enhancement in her vastus intermedius muscle and iliacus muscle. Skin biopsy and pathological examination results were consistent with dermatomyositis.

The patient was diagnosed as RP-ILD with anti-MDA5 Ab-positive dermatomyositis. She was treated with 60 mg/day of oral prednisolone following high-dose corticosteroid (methylprednisolone 1g/day for 3 days), oral tacrolimus (trough concentration 5–10 ng/ml) and IVCY (800 mg/day). Despite the introduction of intensive immunosuppressive treatment, shortness of breath and skin lesions worsened with elevation of serum KL-6 and ferritin levels. The S/F ratio was declined from 466 to 391 on day 3. To prevent her development of respiratory failure, the first session of PE was started three times per week on day 8. PE was performed using 5% albumin as the main replacement fluid. Fresh frozen plasma was administered at the end of the session to prevent

coagulopathy. The plasma volume exchanged in the session was 5500 ml. After the first PE session, the anti-MDA5 Ab, ferritin, KL-6, IL-6, IL-8, and IL-18 blood levels were decreased to 300 index, 53.6 ng/ml, 206 U/mL, 8.0 pg/ml, 13.4 pg/ml, and 305 pg/ml, respectively (Fig. 3). The chest interstitial shadows with consolidation and GGO on HRCT improved after the first PE session (Fig. 1D). No supplementary oxygen was required on day 9. The S/F ratio improved to 471 after 1st session of PE (on day 14).

Although triple therapy was continued thereafter, the blood levels of anti-MDA5 Ab and KL-6 increased once more to 600 U/L and 1531 U/mL, respectively about 2-week post 1st session of PE. On day 36, the 1 L/min oxygen supplement via nasal cannula was restarted because of progressive dyspnea. The patient's skin eruption also became aggravated again. On day 36, a second session of PE was performed three times per week. After the second session of PE concomitant with triple therapy, her skin lesions improved and serum anti-MDA5 Ab and KL-6 levels were promptly decreased to the normal range (Figs. 2 and 3). Although serum KL-6 levels re-increased after 2 sessions of PE, there was no evidence for newly appearance of interstitial shadow. Thereafter clinical symptoms including skin lesions have been maintained stable and serum KL-6 levels gradually deceased to normal range. She was discharged home after a 90-day hospitalization and transferred to another hospital to continue maintenance therapy with low dose prednisolone and tacrolimus.

3. Discussion

Anti-MDA5 Ab-positive patients with clinical amyopathic dermatomyositis (CADM) have typical skin symptoms with low-grade muscle inflammation and frequently develop RP-ILD. The prognosis of anti-MDA5 Ab-positive CADM patients with RP-ILD has been reported to be poor especially in East Asian countries [1,2]. A recent multicenter study reported a high mortality rate of 80% in anti-MDA5 Ab-positive patients with RP-ILD in intensive care units even after conventional immunosuppressive therapy [3]. Three factors, including the severity of the ILD itself, the rapidity of the ILD, and the presence of anti-MDA5 Ab, were associated with short-term prognosis [8]. High titers of anti-MDA5 Ab are related to disease activities and are useful parameters for monitoring RP-ILD with CADM [2,9]. In addition, hyperferritinemia, elevation of serum KL-6 and A-ADO₂, and low PaCO₂ have been reported to be poor prognostic factors [1,6,10].

Herein, we describe two cases of anti-MDA5 Ab-positive CADM with RP-ILD treated with early intervention by PE combined with intensive immunosuppressive agents. Even though conventional immunosuppressive treatment started at admission (day 1) using high-dose corticosteroids plus IVCY and tacrolimus, clinical symptoms including oxygenation and skin lesions, and serum markers worsened within one week from initial treatments in both cases. In order to prevent the development of respiratory failure, we introduced PE on day 8 and simultaneously continued to administration of immunosuppressive agents. After the first session (3 times) of PE, serum titers of anti-MDA5 Ab and KL-6 were dramatically decreased, and oxygenation and skin lesions were improved in both two cases (Fig. 2). Thereafter conventional immunosuppressive treatments were continued, however, serum titers and anti-MDA5 Ab, KL-6 and ferritin levels increased again. We then introduced the 2nd session of PE to suppress disease progressions. After two PE sessions (6 times in total) clinical symptoms were fully recovered, and serum KL-6 and ferritin decreased to the normal range, and more, consolidation and GGO completely resolved on chest HRCT in both cases. Both patients were discharged from hospital without any symptoms.

Several recent reports have demonstrated the efficacy of PE in RP-ILD with anti-MDA5 Ab combined with intensive immunosuppressive treatment [5–7]. PE is usually performed in RP-ILD patients exhibiting resistance to immunosuppressive agents. There are few reports on the effect of early interventional PE combined with immunosuppressive agents in relation to clinical course, serum biomarkers, and chest CT findings. This is the first report of two cases in which early interventional PE combined with intensive immunosuppressive treatment had beneficial effects on RP-ILD patients with anti-MDA5 Ab.

The mechanism of PE in the treatment of RP-ILD with anti-MDA5 Ab remains uncertain. We found a dramatic and prompt reduction in serum anti-MDA5 Ab levels after PE in both two cases. MDA5 protein plays an important role in innate immunity. Environmental triggers such as viral infections activate MDA5, which induces the production of type-1 interferon (IFN), further increasing MDA5 levels and inducing inflammatory mediators [11]. The direct removal of anti-MDA5 Ab by PE may suppress the subsequent induction of MDA5 and inflammatory cytokines. In the present report, anti-MDA5 Ab increased once more and clinical symptoms worsened again after 1st session (three times) of PE. The frequency and timing of PE for RP-ILD patients requires further examination. A recent expert panel recommendation on PE for RP-ILD with anti-MDA5 Ab was not high (grade D) [12]. There is not yet enough data to support the efficacy of PE for RP-ILD with anti-MDA5 Ab. A randomized controlled trial of early interventional PE is needed in order to effectively treat patients with lethal RP-ILD with anti-MDA5 Ab.

4. Conclusion

The early intervention of PE combined with immunosuppressive agents may directly remove anti-MDA5 Ab and then inhibit the

production of inflammatory mediators, which could prevent the lethal development to severe respiratory failure.

Ethics declarations

Ethics approval and consent to participate.
The patient's written consent has been obtained for this publication.
No ethics approval needed since it is a case report.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Patient consent

Mayuko Ishiwari confirm that I have obtained appropriate consent for the publication of this manuscript in Respiratory Medicine Case Reports.

Declaration of competing interest

The named authors have no competing interests, financial or otherwise.

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