



Case report

Rapidly progressive interstitial lung disease due to anti-MDA-5 antibody-positive clinically amyopathic dermatomyositis complicated with cervical cancer: Successful treatment with direct hemoperfusion using polymyxin B-immobilized fiber column therapy



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ARTICLE INFO

Article history:

Received 16 November 2016

Received in revised form

26 November 2016

Accepted 30 November 2016

Keywords:

Anti-melanoma differentiation-associated

gene 5 antibody

Clinically amyopathic dermatomyositis

Rapidly progressive interstitial lung disease

Direct hemoperfusion using polymyxin B-

immobilized fiber column

Cervical cancer

ABSTRACT

The anti-melanoma differentiation-associated gene 5 (MDA-5) antibody is a marker of clinically amyopathic dermatomyositis (CADM) and rapidly progressive interstitial lung disease (ILD) with acute respiratory failure. A 35-year-old woman with cervical cancer showed Gottron's papules, severe hypoxemia, and diffuse ground-glass opacities on chest computed tomography. She was diagnosed with rapidly progressive ILD associated with CADM. Her serum was positive for the anti-MDA-5 antibody. Combination therapy with corticosteroids, immunosuppressants, and direct hemoperfusion using polymyxin B-immobilized fiber column (PMX-DHP) improved her respiratory dysfunction. Eventually, surgery for the cancer was performed successfully. This is the first case to demonstrate the efficacy of PMX-DHP for rapidly progressive ILD with anti-MDA-5 antibody-positive CADM and a malignancy.

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1. Introduction

Clinically amyopathic dermatomyositis (CADM) is characterized by typical skin manifestations of dermatomyositis (DM) with amyopathy or hypomyopathy, and the acute onset of interstitial pneumonia with CADM has been known to develop into rapidly progressive interstitial lung disease (ILD) [1,2]. Rapidly progressive ILD associated with CADM is refractory to intensive therapies such as the systemic administration of high-dose corticosteroids and immunosuppressive agents, leading to a poor prognosis [2,3]. We have previously reported that direct hemoperfusion using polymyxin B-immobilized fiber column (PMX-DHP) therapy in combination with conventional therapy can be effective in the

management of rapidly progressive ILD in patients with CADM [4]. However, the efficacy of adding PMX-DHP therapy when rapidly progressive ILD is associated with CADM and a malignancy remains unclear.

A new autoantibody, the anti-melanoma differentiation-associated gene 5 (MDA-5) antibody (originally referred to as the anti-CADM-140 antibody), has been identified in certain phenotypes of DM, especially CADM [5]. Detection of this antibody is potentially important because its presence may be closely associated with rapidly progressive ILD [5–7]. The anti-MDA-5 antibody is known to be mutually exclusive of anti-aminoacyl-tRNA synthetase (ARS) antibodies, which are representative antibodies detected in DM and polymyositis, and anti-transcriptional intermediary factor 1 gamma (TIF1- γ) antibody, which is closely linked to cancer-associated myositis [6–8]. Recent studies have reported that serial monitoring of serum anti-MDA-5 antibody levels can be useful for assessing therapeutic efficacy, suggesting that this antibody may serve as a marker for disease activity in rapidly progressive ILD with CADM [9]. Furthermore, Fiorentino et al. demonstrated that

Abbreviations: Anti-MDA-5, anti-melanoma differentiation-associated gene 5; CADM, clinically amyopathic dermatomyositis; ILD, interstitial lung disease; PMX-DHP, direct hemoperfusion using polymyxin B-immobilized fiber column.

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<http://dx.doi.org/10.1016/j.rmcr.2016.11.015>

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the anti-MDA-5 antibody was associated with a unique cutaneous characteristic phenotype consisting of skin ulceration and tender papules on the palms, and that the distribution of DM patients with this antibody varied between ethnic groups [10]. In contrast, according to recent findings, the anti-MDA-5 antibody seems to be associated with a relative low risk of malignancy-associated DM [7].

Here we describe a rapidly progressive ILD due to anti-MDA-5 antibody-associated CADM complicated with cervical cancer, who was successfully treated by a combination of pharmacotherapies, PMX-DHP therapy, and resection of cervical cancer.

2. Case report

A 35-year-old woman with a 1-month history of atypical genital bleeding was diagnosed with keratinizing squamous cell carcinoma by a cervical scraping cytology examination and was referred to the Department of Gynecology in our hospital. Pelvic computed tomography (CT) revealed a heterogeneous enhancing mass (62 × 40 mm) in the cervix and the proximal part of the vagina (Fig. 1A). She also presented with dyspnea on exertion that had started 1 month earlier. She was referred to our department and admitted for evaluation and treatment.

Fine crackles were audible in the bilateral middle and lower lung fields. On examination of her hands, hyperkeratotic lesions were seen predominantly involving the palmar surface of the fingers (“mechanic’s hands”), with the presence of scaly erythematous eruptions (Gottron’s papules) on the extensor surface of the proximal interphalangeal and metacarpophalangeal joints. Neurological findings showed no weakness of her proximal muscles on a manual muscle test.

A chest radiography showed marked bilateral volume loss and a diffuse reticular pattern that was more predominant in the lung base than in the apex (Fig. 1B). Chest high-resolution CT scans demonstrated widespread ground-glass opacities with reticulations and traction bronchiectasis in both lungs, suggesting ILD (Fig. 2A and B).

Laboratory findings showed elevated serum lactate dehydrogenase (LDH) and KL-6 levels, at 418 U/l (112–213 U/l) and 906 U/ml (105.3–401.2 U/ml), respectively. In contrast, the levels of creatine kinase and myoglobin were not elevated. The ferritin level was also within the normal range. Blood levels of endotoxin, procalcitonin, and β-D glucan were below the detectable limits. Antinuclear and anti-ARS antibodies, including the anti-Jo-1 antibody, were negative. Interestingly, the anti-MDA-5 antibody was detected by immunoprecipitation assay, although the anti-TIF1-γ

antibody was negative. Bronchoalveolar lavage (BAL) cellular analysis revealed that lymphocytes had increased to 24.5% and neutrophils to 8.5%, whereas the CD4/CD8 ratio in BAL lymphocytes had decreased to 0.15. Arterial blood gas analysis and pulmonary function tests on admission showed decreased PaO₂ (66.4 Torr), decreased vital capacity (60.5% predicted value), and low diffusion capacity of the lung for carbon monoxide (43.3% predicted value). Skin biopsy of a papule developing on the hand showed perivascular infiltrates of inflammatory cells in the dermis, consistent with the characteristic histological changes associated with DM. We therefore diagnosed the patient as having rapidly progressive ILD due to anti-MDA-5 antibody-associated CADM and cervical cancer.

Medical treatment for the rapidly progressive ILD with respiratory failure was needed before surgery for cervical cancer. The patient was administered a combination of a 3-day course of pulse methylprednisolone (1000 mg/day), pulse cyclophosphamide (750 mg/day), and tacrolimus (3–4 mg/day, dose-adjusted for a target trough level of 5–10 ng/ml). However, her respiratory symptoms and signs deteriorated rapidly, and PaO₂/FiO₂ (P/F) ratio decreased from 316.1 (PaO₂ of 66.4 Torr on room air) to 147.6 (PaO₂ of 73.5 Torr on venturi mask at FiO₂ 0.5). PMX-DHP was therefore administered at a flow rate of 100 ml/min for 4 h once daily for 2 successive days (Fig. 3). One week after the PMX-DHP therapy, the P/F ratio improved to 223.8 and serum levels of LDH decreased to 200 U/l. Thereafter, maintenance treatment with tapered corticosteroids and tacrolimus were continued. The patient gradually recovered. Three months after the PMX-DHP therapy, a chest CT showed a remarkable improvement in the bilateral opacities (Fig. 2C and D), and oxygen inhalation was discontinued 3 months later, even during exercise.

Four months after the initial therapy, the dose of prednisolone was reduced to 25 mg/day, and tacrolimus trough level was 8 ng/ml at the dose of 2 mg/day. Thereafter, the patient underwent radical hysterectomy and pelvic lymphadenectomy for cervical cancer. Surgical pathology demonstrated a stage 2b carcinoma. The patient then received postoperative adjuvant chemoradiotherapy. She ultimately recovered to an excellent clinical condition, with no signs of active ILD.

3. Discussion

We reported here a case of anti-MDA-5 antibody-positive and anti-TIF1-γ antibody-negative rapidly progressive ILD complicated with CADM and cervical cancer, which was successfully treated by

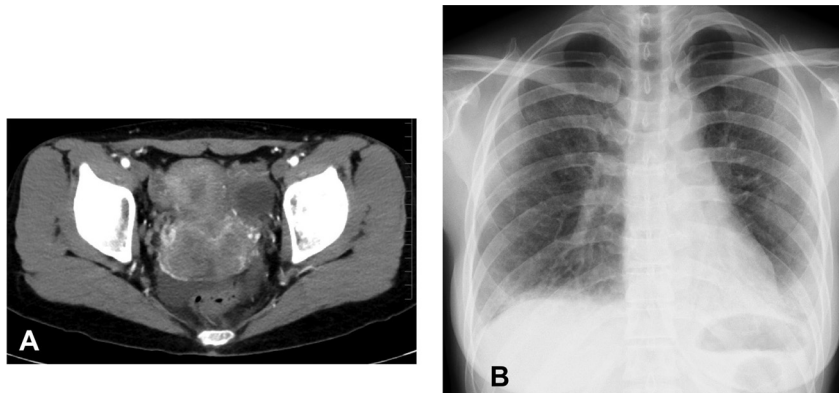


Fig. 1. Pelvic computed tomography (CT) scan and chest radiograph on admission. (A) The CT scan showed a 62 × 40-mm cervical lesion without parametrial invasion. The tumor was mostly localized at the anterior lip of the cervix, which was enhanced heterogeneously. (B) The chest radiograph showed a marked loss of volume and diffuse ground-glass opacities, especially in the lower lung fields.

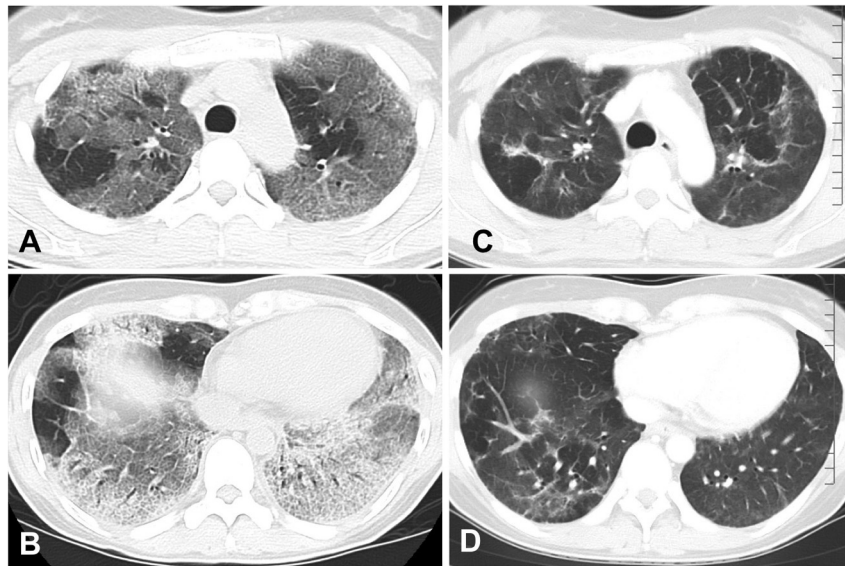


Fig. 2. Changes in chest computed tomography (CT) scan findings before and 3 months after the initial treatment. (A, B) Before the treatment, the CT scan showed bilateral diffuse ground-glass opacities, reticulation opacities, and traction bronchiectasis. (C, D) Three months after the treatment, the ground-glass opacities and traction bronchiectasis had decreased dramatically.

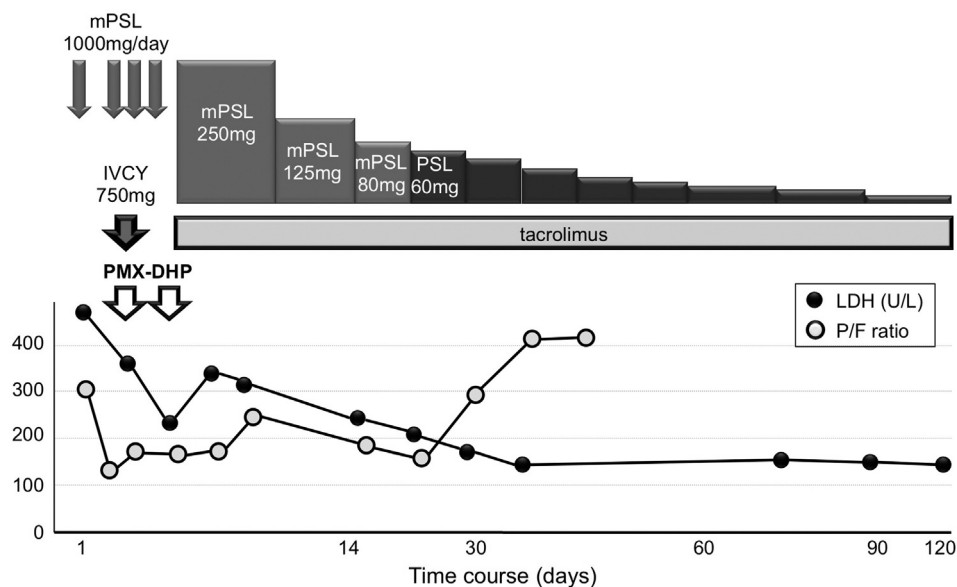


Fig. 3. The clinical course of the patient. mPSL, methylprednisolone; PSL, prednisolone; IVCY, intravenous cyclophosphamide; PMX-DHP, direct hemoperfusion using polymyxin B-immobilized fiber column; LDH, lactate dehydrogenase; P/F, PaO₂/FiO₂.

multimodal therapy, including a combination of high-dose corticosteroids, immunosuppressants, and PMX-DHP, followed by resection of cervical cancer.

Rapidly progressive ILD with acute respiratory failure is one of the most severe and refractory complications of CADM patients, with extremely poor prognosis [1,2]. A triple therapy approach with high-dose corticosteroids, cyclophosphamide, and cyclosporin has emerged as a recommended therapy for refractory interstitial pneumonias associated with CADM [3], but its efficacy remains limited. Previous reports have shown the efficacy of PMX-DHP on acute-onset and refractory ILD, such as acute respiratory distress syndrome and acute exacerbation of idiopathic pulmonary fibrosis [11,12]. The present case suggests that PMX-DHP treatment may assist the effects of the combination therapy of pulse and high-dose

corticosteroids and immunosuppressants in a patient with CADM-associated rapidly progressive ILD even when this complicated by a malignancy. PMX-DHP has been used for the treatment of sepsis to adsorb and eliminate blood endotoxins [11,13,14]. Interestingly, it has been shown to improve pulmonary oxygenation as well as hemodynamic status in patients with acute respiratory distress syndrome in both the presence or absence of blood endotoxins [11,14]. Animal and clinical studies have suggested that another mechanism of the action of PMX-DHP is the direct or indirect removal of activated leukocytes in peripheral blood and/or inflammatory mediators, including proinflammatory cytokines [13,14]. Interestingly, Zou et al. demonstrated that the disease activities of CADM-ILD are related to the serum level of interleukin-8 and the mRNA level of CD11b in circulating neutrophils [15].

Several case reports and retrospective studies have demonstrated that applying PMX-DHP in addition to conventional therapies was effective for the treatment of rapidly progressive interstitial pneumonias with respiratory failure, including CADM [4,12,14]. However, the efficacy of PMX-DHP therapy in combination with conventional therapies remains unclear.

The anti-MDA-5 antibody was initially identified as a novel autoantibody against 140-kDa proteins in CADM patients (hence its original name of “anti-CADM-140 antibody”) [5]. The present case was positive for anti-MDA-5 antibody. This antibody is associated with rapidly progressive ILD and severe cutaneous vasculopathy in patients with DM, particularly in those with CADM [5–7]. A retrospective study by Muro et al. showed that the anti-MDA-5 antibody may be a useful biomarker for ILD with CADM [9]. Another study showed that the 2-year survival rate for anti-MDA-5 antibody-positive patients was lower than that for anti-ARS antibody-positive patients or antibody-negative patients [16]. Thus, the early detection of anti-MDA-5 antibodies in ILD patients with CADM may allow for an early aggressive intervention to decrease fatalities [6,7,16].

The patient in the present case had a combination of cervical cancer, CADM, and rapidly progressive ILD. The anti-TIF1- γ antibody (originally known as the anti-p155 or anti-p155/140 antibody) has been identified as a myositis-specific autoantibody in DM [17]. This antibody is detected in approximately 20%–30% DM patients and 50%–100% cancer-associated DM patients, and is useful for disease management [7,8,17]. Furthermore, the anti-MDA-5 and anti-TIF1- γ antibodies are mutually exclusive, and the anti-MDA-5 antibody identifies a relatively low risk of malignancy-associated DM. Therefore, DM-specific antibodies such as anti-MDA-5 and anti-TIF1- γ antibody define clinically distinct subtypes, and are valuable in predicting outcomes in DM. The present case was negative for the anti-TIF1- γ antibody despite having cervical cancer. To date, case reports on the association between CADM with cervical cancer have been rare [18], and it remains controversial whether this patient's cancer should be considered as relevant or accidental. We are aware of only two other reports of anti-MDA-5 antibody-positive patients with malignancy, CADM, and active ILD [19,20]. One case did not recover from the respiratory failure after the complete removal of thyroid cancer, and the other case (with advanced gastric cancer) could not be treated because of acute respiratory failure. Unfortunately, there was no information regarding the anti-TIF1- γ antibody in either case. In patients with DM as a paraneoplastic syndrome, it is critically important to control the underlying malignancy [17]. In patients with a malignancy and rapidly progressive ILD with CADM, surgical resection of the malignancy is nearly impossible; however, in the present case, a combination therapy of high-dose corticosteroid, immunosuppressants, and PMX-DHP improved the rapidly progressive ILD, and surgical resection of the cancer was successful.

In summary, this report indicates the efficacy of PMX-DHP in combination with corticosteroids and immunosuppressants for the treatment of rapidly progressive ILD in a patient with CADM and cervical cancer. In this case, the anti-MDA-5 antibody suggested rapidly progressive ILD in a patient with CADM, but the anti-TIF1- γ antibody was negative despite the patient's cervical cancer. There are no established treatments for CADM with rapidly progressive ILD and malignancy; thus, further studies are required to determine the diagnostic and therapeutic strategies for CADM with serious complications.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgment

The authors thank Dr. Ran Sasai (Department of Department of Rheumatology and Clinical Immunology, Kyoto University Hospital) for the measurements of anti-MDA-5 and TIF1- γ antibody titers by immunoprecipitation assay in the patient.

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