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Case report

Blood purification in two patients with clinically amyopathic dermatomyositis associated with interstitial lung disease with anti-melanoma differentiation-associated gene-5 antibody (MDA-5)

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ABSTRACT

Patients of clinically amyopathic dermatomyositis associated with rapidly progressive interstitial pneumonia (CADM-RFIP) with positive anti-MDA5 antibody usually presents rapid deterioration and traditional therapy such as cyclophosphamide combined with high-dose prednisone pulse therapy shows no clear benefit at whiles. However, blood purification combined with traditional therapy works according to the literature. We herein report two CADM-RFIP patients administered with DNA immunoadsorption combined with traditional therapy and then reviewed the literature of blood purification in CADM-RFIP patients at home and abroad to date. We emphasize blood purification such as DNA immunoadsorption could apply in the early stage of CADM-RFIP, which can decrease inflammation and allow us more time to control the condition better.

1. Introduction

Clinically amyopathic dermatomyositis (CADM) refers to a special subgroup of dermatomyositis, which shows typical symptoms of dermatomyositis while lacks objective signs and laboratory results such as serum biomarkers and muscle biopsy. Interstitial lung disease (ILD), the most common complication of CADM, are often associated with poor prognosis [1]. Recently, many studies have revealed that CADM patients with positive anti-MDA5 antibodies have a significant correlation with rapidly progressive interstitial pneumonia (RPIP) [2]. Administration with traditional treatment such as cyclophosphamide combined with high-dose prednisone pulse therapy and cyclosporine shows no clear benefit in some prednisone-resistant patients and the condition continues to deteriorate [3]. However, blood purification treatment combined with traditional therapy suggests some effect on CADM-RFIP patients [4]. Here, we describe two cases using DNA immunoadsorption in our department and then reviewed the literature of blood purification in CADM-RFIP patients at home and abroad to date.

1.1. Case one

A 55-year-old man with an eight-month-history of dermatomyositis was admitted to one local hospital for progressive dyspnea and weakness. Without obvious improvement, he went to another hospital. On that admission, he was diagnosed with right pleural effusion, right-side pneumothorax, and interstitial pneumonia and treated with thoracic closed drainage and 8mg methylprednisolone taken orally. Later he was admitted to our hospital because of cold, fever and dyspnea worsening for ten days. Physical examination revealed the temperature was 38.5 °C and he appeared to be in moderate crackles in the lower pulmonary lobes. Besides, lips and fingers cyanosis, mechanic's hand, and Gottron's signs could be found. Arterial blood gas analysis showed FiO_2 21%, PaO_2 45 mmHg, SaO_2 84%, $PaCO_2$33 mmHg. C-reactive protein (CRP) was 56.6 mg/l, anti-MDA5 antibody, anti-RO antibody, and anti-KU antibody were positive but anti-nuclear antibody and anti-Jo 1 antibody were not detected. Initial HRCT revealed peribrochovascular and subpleural consolidation and reticulation in both lungs (both mid to lower lung zone predominance).

Once administered to our hospital, the patient was immediately treated with 8mg/d methylprednisolone combined with 400mg/kg. d immunoglobulin for 3 days, following methylprednisolone 40 mg for 5 days and the condition continued to deteriorate (Fig. 1). Then he was administered with DNA immunoadsorption at a flow rate of 50ml/min with plasma and 180ml/min with blood (DNA280, Jafron Biomedical

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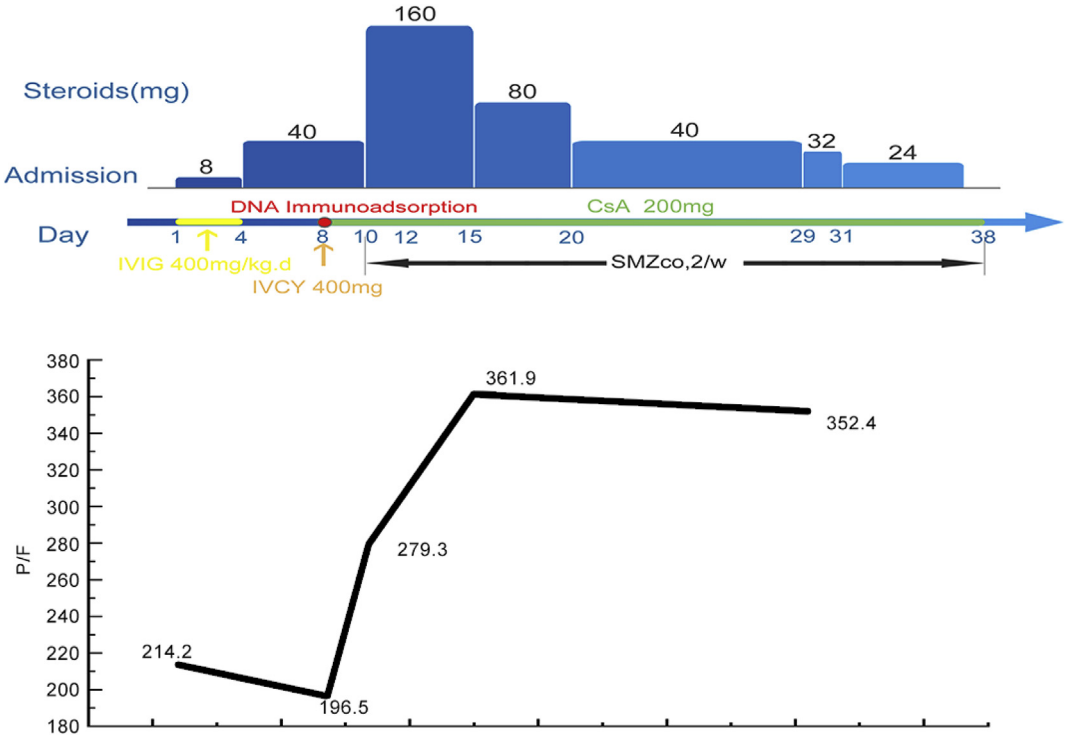

Fig. 1. The therapy of the first patient, CsA: cyclosporine A, IVIG: intravenous immunoglobulin, IVCY: intravenous pulse cyclophosphamide, Steroids: methylprednisolone, SMZco: Trimethoprim/sulfamethoxazole; P/F: PO_2/FIO_2.

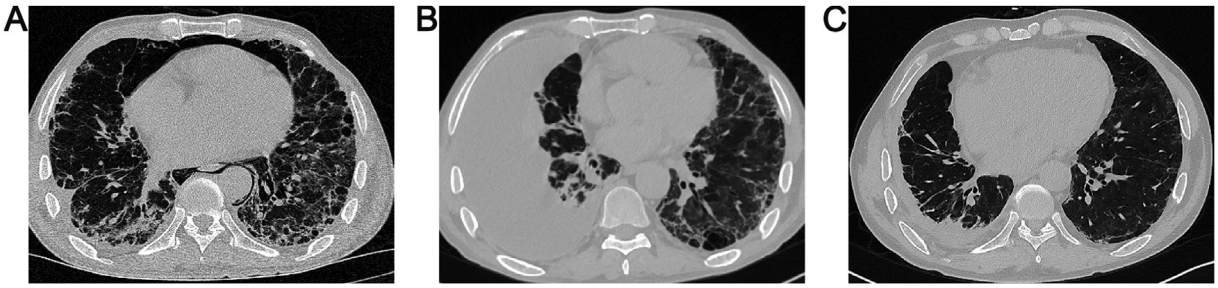

Fig. 2. Changes in HRCT findings of Case 1. A, Before DNA immunoadsorption, reticulation and consolidation could be seen. B: two months later after DNA immunoadsorption, faded reticulation while increased pleural effusion in the left lung could be found; C: two years later after DNA immunoadsorption, reticulation and consolidation evaporated virtually and gradually reduced pleural effusion in the left lung could be found.

Co., Ltd, Zhuhai, China). Later 400mg cyclophosphamide and 160mg/d methylprednisolone were given by intravenous drips. Two weeks later, dyspnea and oxygenation were obviously improved (FiO_2 21%, PaO_2 76 mmHg, $PaCO_2$38 mmHg). He was administered with 1000mg cyclophosphamide per month, 24mg/d prednisone, 200mg/d cyclosporin A and SMZco 2 tablets, twice a week in the maintenance therapy. Three months and two years later re-examine HRCT showed patently reduced reticulations. (Fig. 2).

1.2. Case two

A 57-year-old man previously healthy was admitted to a hospital because of cough and fever for 20 days and empirically administered for suspected bronchitis with intravenous levofloxacin. With no relief of symptoms, he was transferred to our institution for further diagnosis and management. Typical mechanic's hand, Gottron's signs, and basal crackles could be found during the physical examination. Laboratory findings showed CRP was elevated to 89.5mg/L, ferritin was 1567.74ng/ml, anti-MDA5 were positive. In addition, arterial blood gas analysis demonstrated $PaCO_2$ 29 mmHg; PaO_2 65 mmHg; FiO_2 41%. Initial HRCT revealed flocculent shadows, plaques as well as reticulations in bilateral subpleural lungs.

Once admitted to our hospital, he was administrated with 1g methylprednisolone pulse therapy per day for 3 days and 400mg cyclophosphamide (Fig. 3) for rapid progression observed on HRCT. Meanwhile, he accepted plasma exchange of 2200ml to decrease abnormal self-antigens and antibodies. And his oxygen saturation improved slightly ($PaCO_2$ 34 mmHg; PaO_2 72 mmHg; FiO_2 33%). Ten days later his condition worsening again we decided to apply DNA immunoadsorption (DNA280, Jafron Biomedical Co., Ltd, Zhuhai, China). In the following 2 weeks, oxygen requirements decreased (FiO_2 29%, PaO_2 82 mmHg, PaCO2 41 mmHg), cough and dyspnea significantly improved. When he left the hospital, oral methylprednisolone tablets 28mg/day, ciclosporin A 200mg/day, SMZco 2 tablets, 2/week and cyclophosphamide 1g/month were initiated. In our follow-up, his dyspnea aggravated 8 months later and died as his families refused to receive regular re-examination for some reasons.

2. Discussion

Since it was found by Sato in 2003, researches between anti-MDA5 antibodies and dermatomyositis were carried out [5,6]. Recently, some

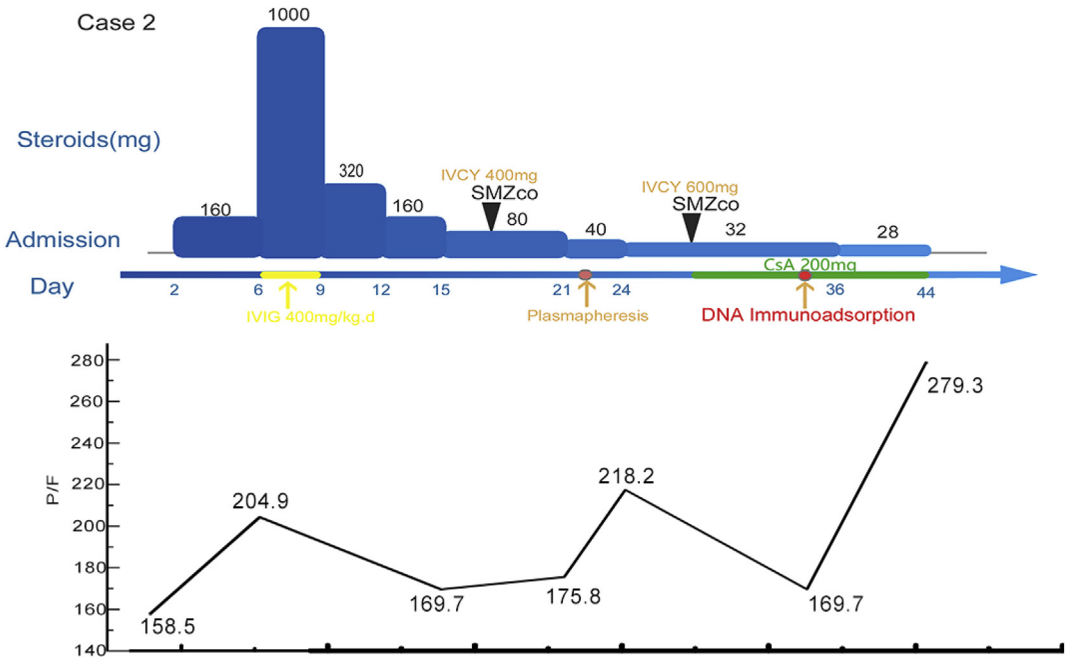

Fig. 3. The therapy of the second patient, CsA: cyclosporine A, IVIG: intravenous immunoglobulin, IVCY: intravenous pulse cyclophosphamide, Steroids: methylprednisolone, SMZco: Trimethoprim/sulfamethoxazole; P/F: PO_2/FIO_2.

components including B cells, autoantigens, and autoantibodies have been found to correlate with disease activity of dermatomyositis [7,8], and therefore may play a part in the pathogenesis of the disease, for example, MDA5 in CADM. Now, anti-MDA5 antibodies are a serologic marker for rapidly progressive interstitial pneumonia complicating CADM [9]. Blood purification, which originates from the dialysis of kidney diseases but has gone beyond the traditional treatment of uremia, is widely used in multiple organ failure and other diseases. The new model of blood purification has presented to use to remove a certain matter, such as plasmapheresis, DNA immunoadsorption or polymyxin B-immobilized fiber column (PMX-DHP) and so on. Especially, DNA immunoadsorption relieved patients immune response by binding to the anti-DNA antibody and other non-specific antibodies warrant us the chance to control the condition [10].

The first CADM-RFIP with anti-MDA5 antibody showed poor effect and rapid progression under traditional strategies. After the immunoadsorption therapy, subjective symptoms and blood gas analysis in oxygenation were significantly improved. The second patient was given plasmapheresis therapy for the first time. Ten days later his condition worsening again, immunoadsorption treatment was selected and his shortness of breath and rash improved.

The success of DNA immunoadsorption in these two patients may derive from the reasons as follows: On the one hand, the lgG of these two patients before and after immunoadsorption respectively were 133.3 to 10.7g/L and 112.7 to 9.5g/L. We hypothesis these two successfully treated patients may result from the removal of some non-specific antibodies by the DNA immunoadsorption. A prevailing notable study [11] suggested that immunoglobulin removal by immunoadsorption significantly decreased the level of anti-dsDNA antibody and disease activity in active SLE, which revealed the relationship between the anti-DNA antibody and immunoglobulin. Furthermore, this study [11] may suggest the potential capacity of DNA adsorption for removing the immunoglobulin from the serum as mentioned [10] previously. On the other hand, the first patient presents anti-Ku antibody in addition to anti-MDA5 antibody. Ku, which is a DNA-binding protein, is associated with the DNA repair [12] and the anti-KU antibody detection in myositis often reveals favorable prognosis [13]. On the basis of this, we determined to adopt DNA adsorption on him and obtained a favorable outcome. The second patient was treated with plasmapheresis firstly but then re-worsened later, the DNA immunoadsorption was chosen based on the first patient experience after obtained the consent of their family.

In searching the database PubMed from 1993 to June. 2019 using terms “anti-MDA5 antibody AND (blood purification OR hemoperfusion OR plasmapheresis OR plasma exchange OR plasma absorption OR immunoadsorption)”, 9 essays [14–22] (8 cases report and 1 article [16]) are implicated in CADM-RFIP with a positive anti-MDA5 antibody, but the patients involved in that article could also found in the other cases reports. For this reason, we just exhibit a total of 10 CADM patients with anti-MDA 5 antibody positive, including ours. The patients’ characters were presented in Supplementary Table 1.

Seven of ten patients (aged from 32 to 71 years) are male and the past course usually sustains 2 weeks to 8 months. Apart from symptoms of cough and dyspnea, Gottron's signs, mechanic's hand, skin rash could be found. However, arthralgia and muscle weakness are rarely few. Laboratory examination indicates a significantly elevated ferritin, LDH, KL-6. In addition, hypoxemia and respiratory failure are found in almost 10 patients. In terms of HRCT findings, abnormal imaging including plaques, consolidation, and ground glass was in bilateral lower lobes distribution in 6 patients and diffuse distribution in 4 patients. Pneumothorax and mediastinal emphysema occurred in 2 patient [21].

Once diagnosed with CADM, most patients were treated with high-dose corticosteroid (1 mg/kg/day)pulse therapy combined with cyclophosphamide and cyclosporin A. During the blood purification, 6 patients [14,15,17,18,21,22] were with direct hemoperfusion using a polymyxin B-immobilized fiber column (one was with PMX only [21]) and two of them died. Four patients were treated with plasma exchange [19–21] and two of them suggested favorable outcome [17,21]. The remained two patients in our department received DNA adsorption and showed ameliorated symptoms. In the maintenance therapy later, 3 patients received methylprednisolone along with cyclophosphamide, two were treated with PMX-DHP/intravenous immunoglobulin with tacrolimus [15,18], one received mycophenolate combined with rituximab [14], one was with tofacitinib [20], and the remainder maintenance therapy can't be found in the essay [19,22]. Ultimately, 8 patients were out of the hospital but Case 2 in our institution died later.

Considering the prognosis factors of the condition, the serum ferritin level, IL-6 [18,22] and nonspecific immunoglubulin other than the titer of anti-MDA5 antibody may be useful to evaluate the reponse to the therapy. In addition, a lower PO_2/FiO_2 and platelets and a higher lactate dehydrogenase could be found in CADM-RFIP with positive anti-MDA5 antibody than those with negative anti-MDA5 antibody [16].

In conclusion, we reported two cases of CDMA-ILD with positive anti-MDA5 antibody adopting DNA immunoadsorption within the active stage of the disease, which alludes some effect in diminishing the inflammatory response and grants us time and opportunity to control the disease.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100896.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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