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Successful treatment of Anti-MDA5 antibody-positive dermatomyositis-associated rapidly progressive interstitial lung disease complicated by pulmonary infection using double-filtration plasmapheresis and haemoperfusion with HA380: A case report and literature review

Abstract

Anti-Melanoma Differentiation-Associated gene 5 (MDA5) antibody-positive dermatomyositis (anti-MDA5+DM) is frequently associated with severe pulmonary complications, including Rapidly Progressive Interstitial Lung Disease (RPILD) and pulmonary infections, both of which are associated with high mortality rate. Therefore, the early identification of RPILD associated with pneumonia is crucial for the effective management of these patients. Here we report a case of a 61-year-old woman diagnosed with anti-MDA5+DM who developed RPILD three weeks after a COVID-19 infection. She was complicated by mixed multi-pathogen lung infections, which were identified through Metagenomic Next-Generation Sequencing (mNGS) of alveolar lavage fluid. After successful treatment with Double-Filtration Plasmapheresis (DFPP) combined with hemoperfusion with HA380, the patient's symptoms significantly improved. Our case and the literature review summarize the efficacy of plasmapheresis for MDA5-DM. To our knowledge, this is the first well-documented case of DFPP and HA380 hemoperfusion in the setting of anti-MDA5+DM with RPILD, providing a novel adjunctive treatment option for patients with this condition.

Keywords: Anti-MDA5 antibody-positive dermatomyositis; Rapidly progressive interstitial lung disease; lung infections; Double filtration plasmapheresis; HA380 hemoperfusion.

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Introduction

Anti-Melanoma Differentiation-Associated gene 5 (MDA5) antibody-positive Dermatomyositis (anti-MDA5+ DM) is a systemic autoimmune disease often associated with severe lung damage. Rapidly Progressive Interstitial Lung Disease (RPILD) is a life-threatening complication of anti-MDA5+ DM associated with a poor prognosis and high mortality. There are currently no established recommendations or guidelines for the treatment of anti-MDA5+ DM with RP-ILD, but the most commonly recommended regimen is a combination of glucocorticoids and immunosuppressants. This typically includes triple therapy with a high-dose corticosteroid, a calcineurin inhibitor and the addition of Intravenous Cyclophosphamide (IVCY). However, studies have shown that patients with MDA5-DM-associated RPILD are resistant to treatment and are susceptible to infections. Recent studies have shown that Plasma Exchange (PLEX) can improve the prognosis of patients with MDA5+ DM suffering from RPILD by removing autoantibodies and inflammatory cytokines. This process creates a therapeutic window for immunosuppressive drugs to take effect, particularly in severe cases or in patients with concurrent infections.

We present a rare case of RPILD associated with anti-MDA5+ DM in a patient complicated by a pulmonary infection. The presence of elevated levels of anti-MDA5 antibodies and multiple pathogenic infections necessitated an aggressive combination

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therapy regimen, which included double filtration plasmapheresis due to plasma allergy, hemoperfusion with HA380, corticosteroids, immunosuppressants, and anti-infectives. To our knowledge, this is the first well-documented case utilizing both Double Filtration Plasmapheresis (DFPP) and hemoperfusion with HA380 in the setting of anti-MDA5+ DM. This case demonstrates for the first time that DFPP can serve as an alternative to traditional plasma exchange in situations of plasma deficiency or plasma allergy. By effectively purifying inflammatory factors, DFPP may represent a viable therapeutic approach for patients with MDA5-DM-associated RP-ILD.

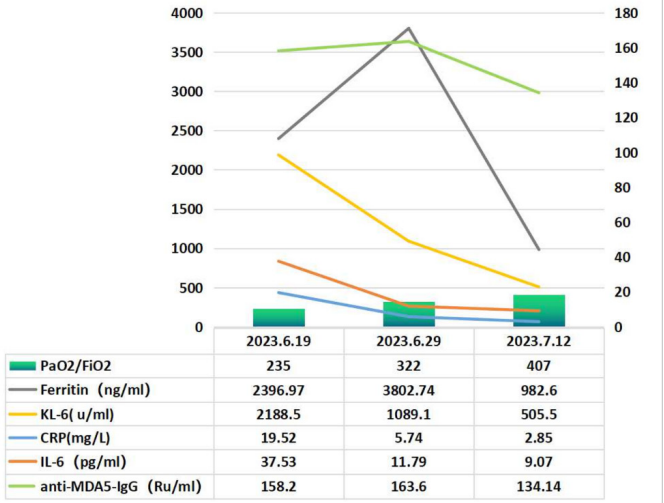
Case presentation

Our patient is a 61-year-old woman presenting with complaints of scattered rashes, fatigue and dyspnea. She was diagnosed with a coronavirus infection one month prior to admission, and three weeks later presented with worsening shortness of breath accompanied by bilateral conjunctival redness. On examination, the patient appeared thin, malnourished, and chronically ill. In particular, she exhibited a violaceous maculopapular eruption on the upper eyelids, the extensor surfaces of the Proximal Interphalangeal (PIP) joints and palms, suggestive of a heliotrope rash and Gottron's papules. Additionally, old ulcers were observed on the dorsal aspect of the Distal Interphalangeal (DIP) joints and the elbow joints. Bilateral conjunctival erythema was also noted. Chest examination revealed Velcro rales over both lung fields. Motor examination with Medical Research Council (MRC) grading scale revealed symmetric proximal weakness in the lower extremities, muscle strength of the lower extremities was graded 4/5. Chest Computed Tomography (CT) scan showed progression of interstitial lung disease. Metagenomic next-generation sequencing of alveolar lavage fluid identified multiple pathogens: Candida albicans (accession number 6517), Enterococcus faecalis (accession number 783) and Aspergillus fumigatus (accession number 841). The Galactomannan (GM) test of the alveolar lavage fluid was positive.

The patient was diagnosed with MDA5-DM, characterized by typical heliotropic and Gottron rashes, along with high titers of anti-MDA5 antibodies. This condition was complicated by RPILD, which presented with worsening respiratory symptoms and radiological progression. Anti-infective and anti-inflammatory treatments improved the patient's rash and alleviated shortness of breath; however, ferritin levels increased. The patient had a history of plasma allergy. To manage the patient's elevated inflammatory state, double filtration plasmapheresis and hemoperfusion with HA380 were initiated. Subsequently, levels of C-Reactive Protein (CRP), interleukin-6 (IL-6), KL-6, and ferritin decreased significantly (Figure 1). A chest CT scan revealed that the lung lesions had resorbed compared to previous imaging (Figure 2). After discharge from the hospital, the patient was prescribed methylprednisolone 20 mg daily, tacrolimus 1 mg q12h, and thalidomide 50 mg qn.

Discussion

MDA5-DM has a complex clinical phenotype. In contrast to other subtypes of dermatomyositis, those who test positive for anti-MDA5 antibodies often develop RPILD with a high mortality rate [1,2]. Identifying RPLD as an initial manifestation of MDA5-DM is essential for patient survival [3]. High levels of Lactate Dehydrogenase (LDH), Krebs von den Lungen-6 (KL-6), Serum Ferritin (SF), Interferon-α (IFN-α) and interleukin-6 (IL-6), anti-MDA5 titers, lymphocytopenia, and positive RO-52 antibody are generally considered to indicate a poor prognosis [4-7].



	2023.6.19	2023.6.29	2023.7.12
PaO2/FiO2	235	322	407
Ferritin (ng/ml)	2396.97	3802.74	982.6
KL-6(u/ml)	2188.5	1089.1	505.5
CRP(mg/L)	19.52	5.74	2.85
IL-6 (pg/ml)	37.53	11.79	9.07
anti-MDA5-IgG (Ru/ml)	158.2	163.6	134.14

Figure 1: Diagnostic laboratory values during the patient's hospital stay. Ferritin levels increased after anti-infective and anti-inflammatory treatments since 2023.6.19 whereas oxygenation index and levels of C-reactive protein (CRP), interleukin-6 (IL-6), KL-6, and ferritin all improved significantly following double filtration plasmapheresis and hemoperfusion with HA380 in 2023.6.29.

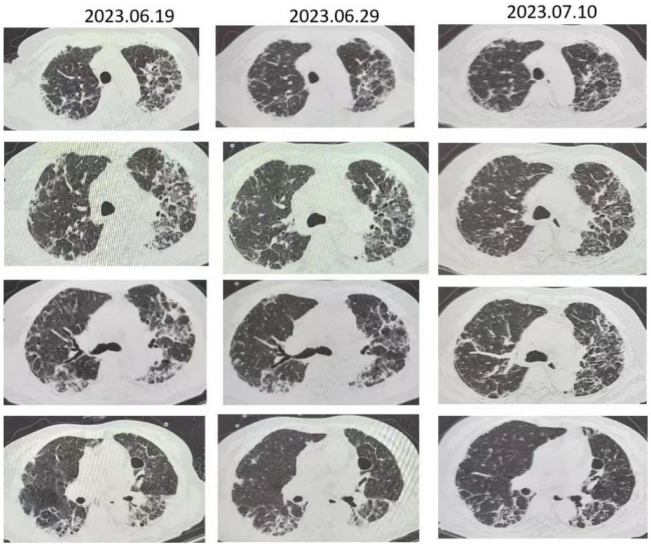


Figure 2: Chest CT at different points in time. The lung lesions shown by chest CT had gradually resorbed compared to previous images.

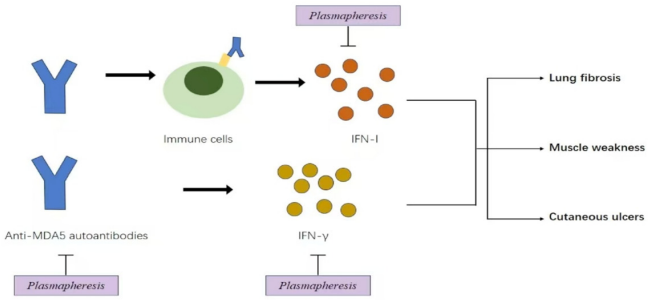


Figure 3: Plasmapheresis targeting cytokines in MDA5-DM. Interaction between the autoantibody and the ectopic antigenic target may result in chronic activation of the type I interferon (IFN-I) signaling pathway. Autoantibodies can also drive IFN-γ synthesis relying on monocytes. These cytokines contribute to lung fibrosis and cutaneous ulcers, which can be effectively removed by plasmapheresis.

Table 1: Reported cases of applying plasmapheresis to MDA5-DM.

Author/Year	Age/Sex	Complication	Treatment	Prognosis
M G Silveira et al. [36]	42/M	RP-ILD	Methylprednisolone, tacrolimus, hemoperfusion with polymyxin B, plasmapheresis	Improved
Lu C et al. [33]	31/M	RP-ILD	Methylprednisolone, human immunoglobulin, six cycles of plasma exchange	Mitigated
Yuya Fujita et al. [30]	56/F	Hemophagocytic Syndrome, ILD	Cyclophosphamide pulse therapy, plasmapheresis	Improved
Dai Kishida et al. [32]	29/F	ILD, macrophage activation syndrome	Methylprednisolone, prednisolone (PSL) and tacrolimus (TAC), cyclosporine A (CyA), cyclophosphamide, plasmapheresis	Stable
Noriko Sasaki et al. [28]	70/F	RP-ILD	40mg of PSL, 3mg of tacrolimus, 650mg of intravenous cyclophosphamide (IVCY), PE (3 times/week)	Improved
Endo Y et al. [29]	71/F	RP-ILD, cytomegalovirus (CMV) infection	Corticosteroids, cyclophosphamide, and calcineurin inhibitor, PE 3times/ week	Relieved
Akira Yamagata et al. [37]	60/F	rapidly progressive interstitial pneumonia (RPIP), cytomegalovirus (CMV) reactivation, subcutaneous hematoma	mPSL pulse therapy, IVCY, CyA, seven sessions of therapeutic plasma exchange (TPE)	Improved
Akira Yamagata et al. [37]	60/M	RPIP, CMV reactivation, Subcutaneous hematoma	mPSL pulse therapy, IVCY, CyA, eight sessions of TPE	Improved
Akira Yamagata et al. [37]	62/F	RPIP, CMV reactivation	mPSL pulse therapy, IVCY, TAC, seven sessions of TPE	Improved
Daisuke Hiraoka et al. [31]	71/M	ILD, rheumatoid arthritis (RA), fungal infection, CMV reactivation	Steroids, IVCY, TAC, voriconazole, TOF, PE (twice a week for five weeks), ganciclovir and valganciclovir	Improved
Tomohiro Saito et al. [35]	62/F	RP-ILD	mPSL pulse, PSL, IVCY, Tac, CyA, IVIG, 10 sessions of TPE, 2 sessions of direct hemoperfusion using a polymyxin B-immobilized fiber column (PMX-DHP)	Alive
Tomohiro Saito et al. [35]	46/F	RP-ILD, autoimmune-associated hemophagocytic syndrome	mPSL pulse, PSL, IVCY, Tac, CyA, IVIG, 9 sessions of TPE, 2 sessions of PMX-DHP	Alive
Tomohiro Saito et al. [35]	56/F	RP-ILD	mPSL pulse, PSL, IVCY, CyA, 10 sessions of TPE	Alive
Tomohiro Saito et al. [35]	46/M	RP-ILD	mPSL pulse, PSL, IVCY, Tac, MMF, rituximab (RTX), 14 sessions of TPE	Alive
Tomohiro Saito et al. [35]	59/M	RP-ILD, tacrolimus-induced posterior reversible encephalopathy syndrome	mPSL pulse, PSL, IVCY, CyA, IVIG, RTX, 4 sessions of TPE, 2 sessions of PMX-DHP	Dead
Tomohiro Saito et al. [35]	67/F	RP-ILD, acute respiratory distress syndrome with pneumothorax and mediastinal emphysema	mPSL pulse, PSL, IVCY, CyA, 3 sessions of TPE, 1 session of PMX-DHP	Dead
Ciaglia K et al. [3]	4/F	RP-ILD, pulmonary hemorrhage, acute respiratory failure	Steroids, plasmapheresis, tofacitinib, intravenous immunoglobulin, rituximab	Stable
Bradley J Peters et al. [34]	52/F	RP-ILD, hypoxemic respiratory failure, pneumonia	Corticosteroids, cyclophosphamide, immune globulin, TPE, enoxaparin	Stable

Viral infection is a significant precipitating factor for MDA5-DM and RPILD. Epidemiological studies conducted in Japan and France have suggested that viral infections may serve as potential triggers for MDA5-DM [8-11]. MDA5, a cytoplasmic antiviral protein, is reported to increase in response to type 1 Interferon (IFN) and other cytokines produced by viruses, which may be one of the initiators of MDA5-DM [12,13]. Some individuals have exhibited clinical symptoms of MDA5-DM following a COVID-19 infection or vaccination [14-17]. In this case, the patient was infected with the coronavirus three weeks before her condition worsened. Although her symptoms of fever and shortness of breath improved and the virus became undetectable through treatment, the patient experienced a resurgence of shortness of breath, rash, and bilateral conjunctival redness three weeks later. Laboratory findings, chest CT scans and multidisciplinary discussions indicated that the patient's dermatomyositis had progressed, resulting in the development of a new pulmonary lesion identified as interstitial pneumonia, which was associated with progressing interstitial pneumonia related to dermatomyositis. The exacerbation of the patient's condition was most likely induced by the coronavirus infection.

Although no evidence of pulmonary infection was found in the laboratory tests and sputum examinations, the patient was at high risk of infection due to the use of glucocorticoids and immunosuppressants to control ILD. To comprehensively evaluate the disease, bronchoscopy was performed, and multi-pathogens were detected by mNGS of the alveolar lavage fluid. Although the chest CT did not reveal any invasive lung lesions caused by Aspergillus infection, the patient's immunocompromised status, high pathogen sequence load, and positive GM test of the alveolar lavage fluid suggested that the patient may have early-stage pulmonary Aspergillus infection that had not yet resulted in observable changes on the chest CT. This underscores the importance of using mNGS of the alveolar lavage fluid to identify concurrent pulmonary infections in patients with MDA5-DM-associated RPILD, which is crucial for guiding subsequent therapeutic regimens and determining prognosis.

Recent studies have shown that patients with MDA5-DM-associated RPILD are resistant to treatment and have a poor prognosis. Despite adequate conventional treatment with a combination of corticosteroids, calcineurin inhibitors and either cyclophosphamide or mycophenolate mofetil, the six-month mortality rate is as high as 40% to 60% [18-20]. The pathogenesis of MDA5-DM may involve contributions from T cells, B cells, neutrophils, macrophages, natural killer cells and over-activation of the type I interferon pathway [21-24]. Given the role of type I interferon and the elevated inflammatory status in some patients, there have been ongoing efforts to treat individuals

with MDA5-DM with JAK inhibitors; however, most studies have focused on patients with mild to moderate disease in the early stages. The hyperinflammatory state observed in some patients with MDA5-DM predisposes them to lung damage, indicating a poor prognosis. Plasma exchange is used as a rescue therapy for many severe rheumatic diseases by removing pathogenic substances [25], including inflammatory cytokines and chemokines, from the plasma (Figure 3). It can also be used as an adjunctive therapy in the management of refractory or intractable disease [26].

A Japanese study found that plasma exchange can improve the prognosis of RPILD or active infections associated with MDA5-DM [27]. Another study suggested that the early initiation of plasmapheresis combined with comprehensive immunosuppressive therapy was effective for patients with refractory DM or DM associated with RPILD [28]. We identified 18 case reports in the literature in which plasmapheresis was used to treat MDA5-associated DM, as briefly summarized in Table 1 [3,28-37]. Of the eighteen cases, only one patient was a child. The median age of the patients was 57.5 years and twelve were female. All patients were diagnosed with ILD, 15 of which presented with RPILD, and 6 patients had co-infections. Five patients received polymyxin B haemoperfusion. Two patients died of respiratory failure and sixteen survived suggesting that PE combined with immunosuppressive therapy may be a promising treatment for patients with refractory MDA5-DM-associated RPILD.

However, plasma exchange requires a large amount of plasma and incurs high cost, and it also carries the risk of infections and allergic reactions. Additionally, it should be noted that not all medical facilities have the necessary equipment and trained staff to perform PE [31]. Double Filtration Plasmapheresis (DFPP) is a selective plasma component separation therapy that utilizes a double filter system. DFPP selectively removes cytokines and pro-inflammatory markers and has been widely used in a variety of autoimmune diseases and pancreatitis [38,39]. However, the efficacy of DFPP and hemoperfusion in patients with MDA5-DM remains unclear.

In this case, after anti-inflammatory and anti-infective treatment, the patient's shortness of breath improved and the levels of CRP, KL-6 and IL-6 decreased. However, the patient's ferritin levels remained elevated, indicating a persistent high inflammatory state. Due to the patient's allergy to plasma exchange, double filtration plasmapheresis and hemoperfusion with HA380 were added to the initial treatment plan to address the hyperinflammatory state. Inflammatory markers, including ferritin, decreased significantly, and both the patient's symptoms and chest CT showed marked improvement following this treatment.

Conclusion

This case suggests that double filtration plasmapheresis and haemoperfusion with HA380 may serve as an alternative to conventional plasmapheresis for alleviating the hyperinflammatory state associated with MDA5-DM-associated RPILD, particularly in cases of plasma deficiency or plasma allergy. It may also be an effective treatment for patients with refractory MDA5-DM-related RPILD, especially those complicated by severe infections. To our knowledge, this is the first study to use DFPP combined with haemoperfusion with HA380 in MDA5-DM-associated RPILD. However, as this is a case report, further validation is needed through multicentre prospective studies with larger sample sizes.

Declarations

Ethical statement: This study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (approval number:2022K013).

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Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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