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Case Report

Double Filtration Plasmapheresis Rescued a Severe Dermatomyositis Patient Resistant to Glucocorticoids: A Case Report and Review of the Literature

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ABSTRACT

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by myositis and typical skin symptoms. The first-line therapies are glucocorticoids. However, these are not effective in some patients. In this case, we reported a severe DM patient resistant to gluococorticoids treated with double filtration plasmapheresis (DFPP). The clinical typical skin symptoms, blood routine, renal function, serum muscular enzymes, and muscle strength was compared before and after DFPP. DFPP combined with glucocorticoids remarkably improved clinical symptoms such as skin rash, proximal muscle weakness, and dysphagia in this patient, significantly reducing serum enzymes, while blood routine and renal function did not change dramatically during therapy. DFPP can be used for the rescue treatment of steroid-resistant severe DM. This combination therapy is a rescue therapy in acute phase and preventing severe complications.

Keywords: Dermatomyositis, Double filtration plasmapheresis, Glucocorticoid

Introduction

Dermatomyositis (DM) is a group of autoimmune connective tissue diseases characterized by idiopathic inflammatory myopathy and characteristic skin manifestations [1]. The etiology is unknown and may be related to genetic, infectious, immunologic and environmental factors. The clinical manifestations are involved in skin and muscle. The skin manifests as edematous purple-red patches with different degrees around orbit centered on eyelids, fuchsia pimples on the extremities, elbows, knees, especially the metacarpophalangeal joints and interphalangeal joints. The muscle manifests as proximal limb muscles, scapula and pelvic muscle weakness, pain, tenderness and exercise pain. When the pharynx and upper esophageal muscles are involved, hoarseness and dysphagia may occur; when the esophageal and respiratory muscles are affected, dysphonia and dyspnea may occur; when the heart muscle is involved, heart failure occurs [1]. Glucocorticoids are commonly used as first-line treatment of DM; in severe cases, immunosuppressive therapies and

intravenous immunoglobulins (IVIG) can also be used. In this case, we will report a woman who were resistant to regular glucocorticoids and IVIG, and double filtration plasmapheresis (DFPP) rescued her.

Case Report

General information

We report on a 38-year-old woman, who admitted to our hospital on March 22, 2018 for weakness and pain in the extremities especially proximal muscles, erythema in her face and extremities for one month, and dysphagia for one week. A month ago, the patient had myalgias in the limbs accompanied by the edema of the extremities without any reason. The symptoms aggravated gradually and relieved after rest. Multiple heliotrope rashes on the eyelids, forehead, cheeks, bilateral metacarpophalangeal, interphalangeal and hip joints (called Gottron sign), accompanied by pruritus. She felt weak, squatting difficulty, myalgias and edema of extremities aggravated after exercise. Her hands became purple after cold. A week ago, she had dysphagia, and could only eat a liquid diet.

Physical examination

Her height was 158cm and weight was 60kg. Her vital signs on admission were as follows: body temperature was 36.6°C; pulse: 86 beats per minute; respiratory rate: 20 breaths per minute; blood pressure: 117/88 mmHg. The patient was conscious and appeared cachectic. Edematous heliotrope rash on both sides of the periorbital, multiple heliotrope rashes on the forehead, cheeks, hands and bilateral hip joints. No swelling of superficial lymph nodes in the whole body. Cardiopulmonary auscultation showed no abnormalities. The abdomen was soft and flat. The skin of the extremities was mildly edematous. The strength of the proximal muscle of upper and lower limbs was grade 3 and the distal muscle strength was grade 4. Muscle tension was generally normal.

Laboratory examinations

On admission, the blood routine showed mild anemia. Urine routine and stool routine were negative. Blood biochemical examinations revealed that serum albumin and globulin were normal. The results of routine renal function were normal. Serum muscular enzymes including aspartate aminotransferase (AST), creatine kinase (CK), lactate dehydrogenase (LDH), creatine kinase isoenzyme (CK-MB) were all elevated. The complete sets of autoimmune antibodies were negative. Immunoglobulin and complement factor-4 (C4) were normal. Complement factor-3 (C3) was mildly decreased (Table 1). The erythrocyte sedimentation rate (ESR) was elevated, at 29 mm/h. Enterovirus RNA was positive. These examinations were routine tests and used for expelling other autoimmune diseases.

Special examinations

Electromyography (EMG): Relaxation: No abnormal spontaneous discharge was observed in the examined muscles; Light contraction: The average time limit of the motor unit potential of examined muscles with short duration and low amplitude (21%-33%), and the polyphasic wave increased (28%-50%). Vigorous contraction: The examined muscles were simple to mixed, with an average voltage of 1-2 mV. The examined nerve motor conduction velocity was normal. It was an electromyogram of myogenic lesions. Magnetic resonance imaging (MRI): Extensive edema of bilateral gluteus maximus, pelvic floor muscles, and thigh muscles. PET-CT: There were no apparent signs of malignant tumor lesions in the whole-body detection site. Muscle metabolism in the neck, abdominal wall, pelvic floor and limbs were increased, subcutaneous edema in both hips, which indicated benign lesions; bilateral lymph nodes in the neck and axilla are enlarged, but with no high metabolism, which indicated non-specific changes; breast enlargement; left lower lobe fibrosis; bilateral pleural adhesions; gallbladder enlargement (Figure 1). On March 27th, a chest high-resolution computed tomography (HRCT) scan showed: lungs had a clear texture and patchy blur under the pleura in the outer base of the left lower lobe (Figure 2A). On April 5th, the chest HRCT was reviewed: The soft tissue density of the right middle lobe was observed. The central leaf showed patchy blur and the infectious lesion was considered. The base of the left lower lobe was similar to the previous one (Figure 2B).

Drug treatments

From March 23rd to April 5th 2018, 60 mg intravenous

Table 1: Laboratory examinations on admission.

Blood routine	Urine routine	Stool routine
WBC 3.7X10^9/L	Urine protein(-)	soft, yellow stool
RBC 3.31X10^{12}/L	Urine occult blood (-)	occult blood (-)
Hb 102 g/L	Urine ketone (-)	
PLT 163X10^9/L	Urine white blood cell (-)	
Neutro 67.8%		
Blood biochemistry	**Autoimmunity**	**Immunoglobulin and complement**
Total protein 58 g/L	ANA 1:100	IgE 22.95 IU/ml
Albumin35.9g/L	Anti-cardiolipinAb(-)	IgG 10.4 g/L
Globulin 22.1 g/L	Anti-n RNP(-)	IgA 2.52 g/L
PreAlbumin0.151g/L	Anti-SmAb (-)	IgM 1.59 g/L
BUN 13.93 mg/dL	Anti-SSA Ab (-)	C3 0.683 g/L
Cr 0.486 mg/dL	Anti-SSB Ab(-)	C4 0.173 g/L
UA 3.56 mg/dL	Anti-Scl-70 Ab (-)	
CK 2524 U/L	Anti-JO-1Ab (-)	
LDH 666 U/L	Anti-ds DNA Ab (-)	
AST 143 U/L	Anti-GBM Ab (-)	
CK-MB 32.1 ng/ml	ANCA (-)	

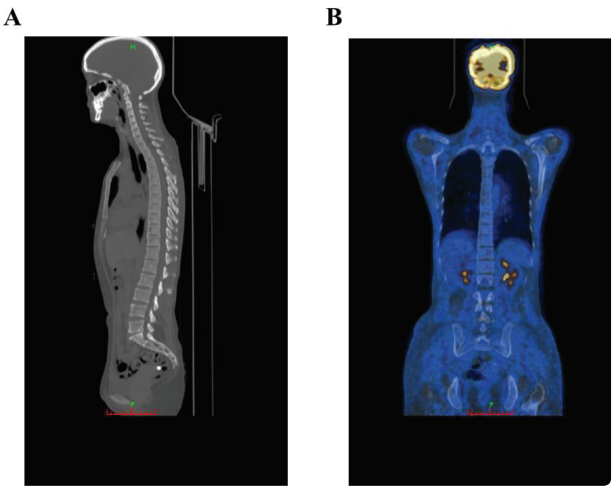

Figure 1: PET-CT scan. There were no apparent signs of malignant tumor lesions in the whole-body detection site. A. Sagittal view. B. Coronal view.

methylprednisolone (1 mg/kg/day) was administered to the patient. When the disease was exacerbated on April 6th, the dose of intravenous methylprednisolone increased to 120mg, while 10g intravenous immunoglobulins (IVIG) was added concomitantly for five consecutive days. During the treatment, the patient developed cough, and coughed chartreuse phlegm, the chest HRCT scan showed pneumonia and antibiotic therapy was initiated. Firstly, levofloxacin was used intravenously for several days. However, the infections could not be controlled well, it changed to meropenem 1000mg twice daily after April 3rd.

Double filtration plasmapheresis

On April 12th, due to dysphagia and systemic symptoms were aggravated, the patient was placed a catheter through the right internal jugular vein for DFPP. We carried out DFPP by the Braun Diapact continuous blood purification device, and used the Asahi Kasei first membrane type plasma separator OP-08W and the secondary membrane type plasma component separator EC-20W to separate pathogenic substances every other day for 6 sessions. The replacement fluid consisted of 40g human blood albumin, 550ml saline and 200ml fresh frozen plasma were added at each session.

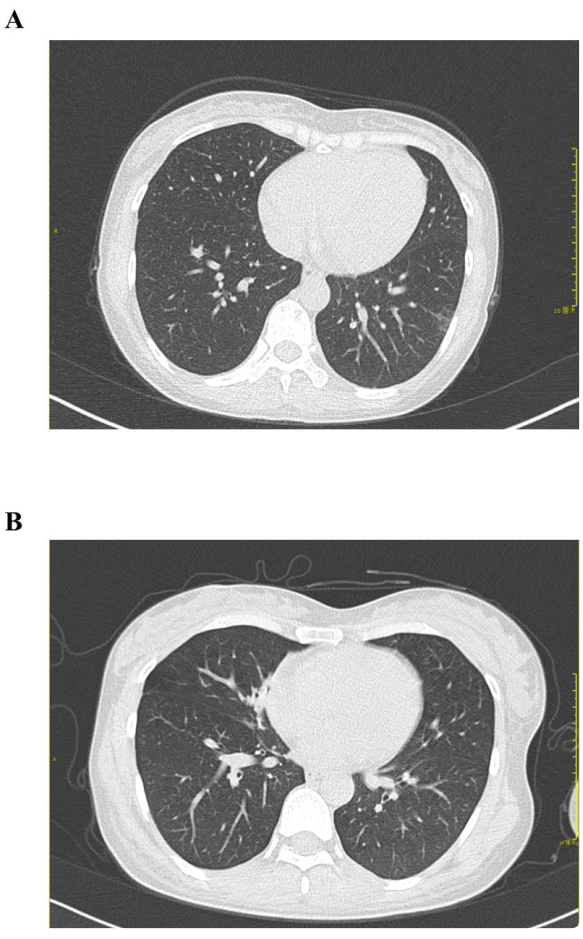

Figure 2: Chest High-Resolution Computed Tomography (HRCT) scan. A. Lungs had a clear texture and patchy blur under the pleura in the outer base of the left lower lobe. B. The soft tissue density of the right middle lobe was observed. The central leaf showed patchy blur.

Observational items

Clinical manifestations, blood routine, renal function, serum muscle enzyme and muscle strength improvement, complications and adverse reactions were noted before and after treatment.

Results

Improvements of clinical symptoms

Muscle soreness and edema of extremities, dysphagia, edema around the eyelids, and rash with pruritus were aggravated before DFPP treatment, although glucocorticoids and IVIG were used. These symptoms were alleviated gradually or even disappeared after DFPP treatment.

Blood routine changes

During the treatment, the patient developed a pulmonary infection, and the blood routine showed an increase in white blood cells and thrombocytopenia (Figure 3A and D). There was no significant change in red blood cells and hemoglobin (Figure 3B and C). After the corresponding anti-infective treatment, the indicators eventually returned to normal.

Changes in serum albumin and renal functions

During treatment, the patient's albumin has been at a low level, creatinine and urea nitrogen levels are at normal or low levels, which may be related to nutritional difficulties caused by dysphagia (Figure 4). The renal function is normal during treatment.

Changes in serum muscular enzymes

During treatment, serum enzymes including AST, CK, LDH, CK-MB, and other indicators decreased when started to use steroid therapy, and then gradually increased, reaching the highest peak on April 12. After DFPP treatment, these muscular enzymes fell progressively (Figure 5). It is demonstrated that DFPP is effective for the recovery of serum enzymes.

Improvements in muscle strength

Before the treatment of DFPP, the proximal muscles of both upper and lower limbs of the patient were grade 3, and it was difficult to resist the external force. The distal muscles of both upper and lower limbs had muscle strength of grade 4, which only resisted a weak external force. After 6 sessions of DFPP treatment, the muscle strengths of this patient were all recovered to grade 5.

Discussion

Idiopathic inflammatory myopathies (IIMs), also known as myositis, are a group of diseases characterized by chronic inflammation and weakness of skeletal muscle. In addition to skeletal muscle, it also affects the skin, heart, lungs and gastrointestinal tract. According to clinical manifestations and histopathology, it can be classified in to polymyositis (PM), dermatomyositis (DM), sporadic inclusion-body myositis (sIBM), nonspecific myositis, and immune-mediated necrotizing myopathy (IMNM) [2,3]. Among them, DM often has an acute or subacute onset, which is usually characterized by typical cutaneous lesions, symmetric proximal muscles weakness, and elevated muscle enzymes. It can be seen in adults and children, more commonly in women, often involving multiple organs. DM is usually associated with tumors and other connective tissue diseases.

The pathogenesis of DM is related to the activation of T and B cells, so glucocorticoids and immunosuppressive therapy are effective.

Glucocorticoids are considered as the first-line treatment of DM. Regular administration of prednisone is 1mg/kg/d at least four weeks, then slowly tapered. In some severe cases, methylprednisolone

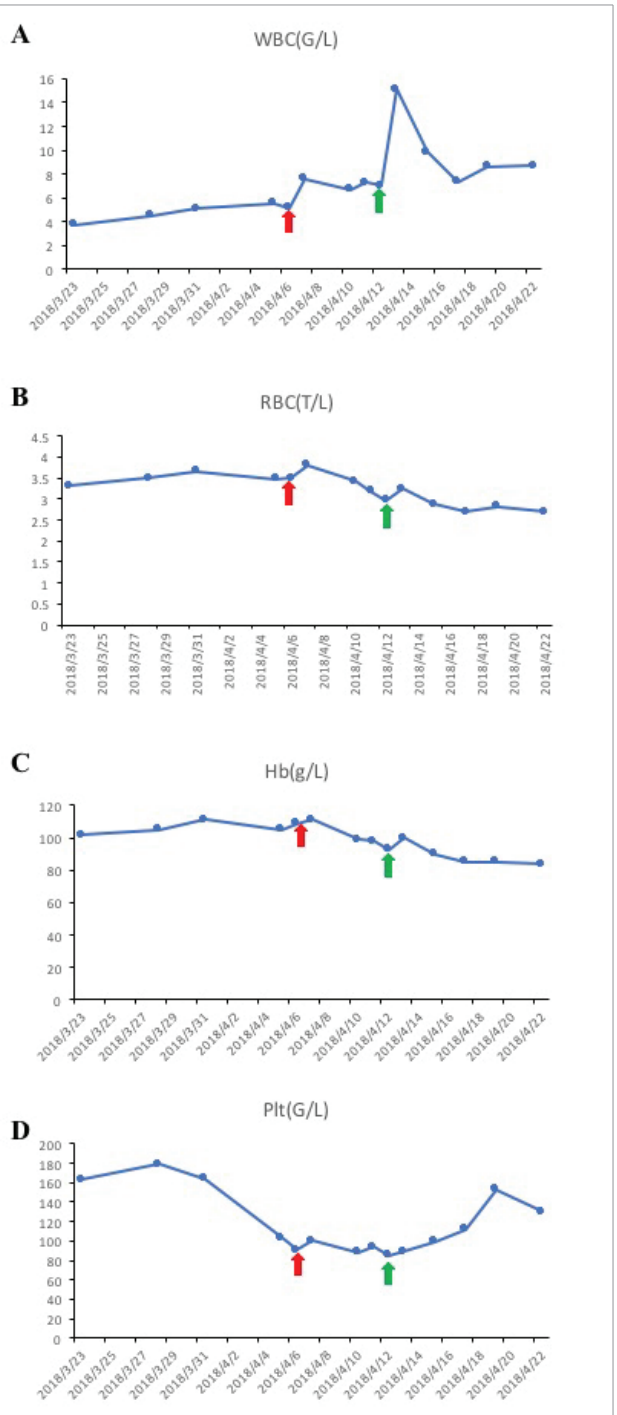

Figure 3: Blood routine results during treatment. A. The changes of white blood cells. B. The changes of red blood cells. C. The changes of hemoglobin. D. The changes of platelets. WBC: white blood cells; RBC: red blood cells; Hb: hemoglobin; Plt: platelets. Red arrow indicates the time of the increase of steroid; green arrow indicates the start time of DFPP.

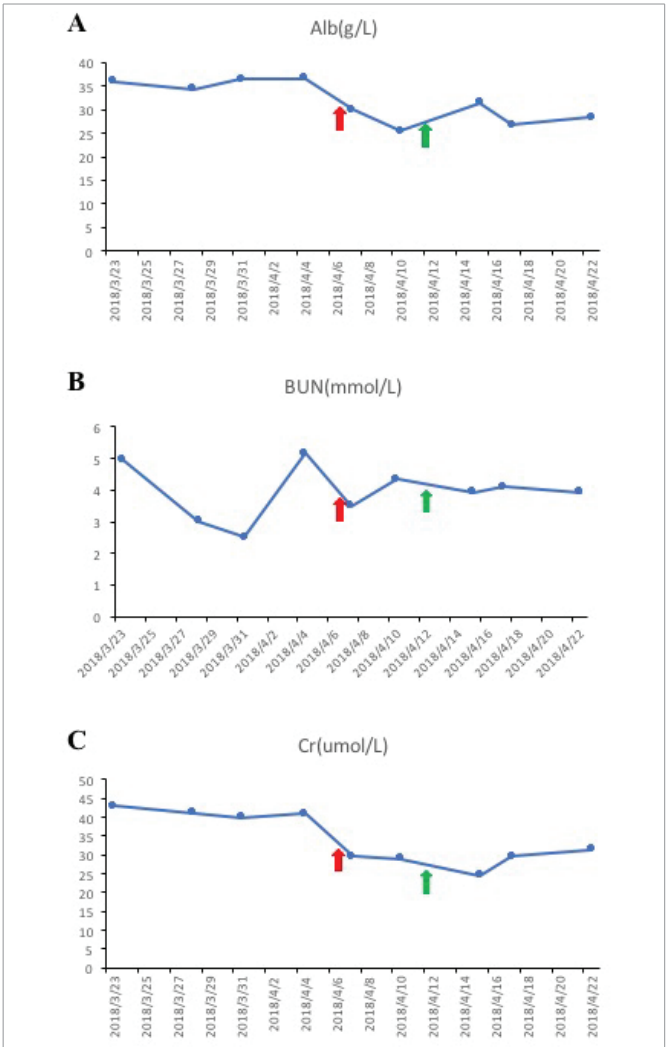

Figure 4: Changes of serum albumin and renal functions during treatment. A. The changes of serum albumin. B. The changes of blood urea nitrogen. C. The changes of creatinine. Alb: albumin; BUN: blood urea nitrogen; Cr: creatinine. Red arrow indicates the time of the increase of steroid; green arrow indicates the start time of DFPP.

500-1000 mg can be given for three days before starting oral regular doses of prednisone. Since some cases are refractory and resistant to corticosteroids, second-line therapies are usually needed to control the activities of the diseases, such as methotrexate, azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, IVIG, topical steroids. New therapies such as anti-CD20 antibody (rituximab), anti-TNF-a antibody, anti-interferon-alpha antibody (sifalimumab), recombinant human IL-1alpha receptor (Anakinra) and Janus kinase inhibitors have also been evaluated [4]. Intravenous immunoglobulin (IVIG) has also been proved to be effective for the refractory DM [5]. Early treatment with glucocorticoids and immunosuppressive agents has a higher remission rate, but some patients still have a poor prognosis. The most common cause of death is respiratory failure, usually due to severe interstitial pneumonia or aspiration pneumonia caused by pharyngeal and esophageal muscle weakness [6].

Therapeutic plasma exchange (TPE) refers to the separation of plasma and blood cells from a patient's blood by a blood pump, using

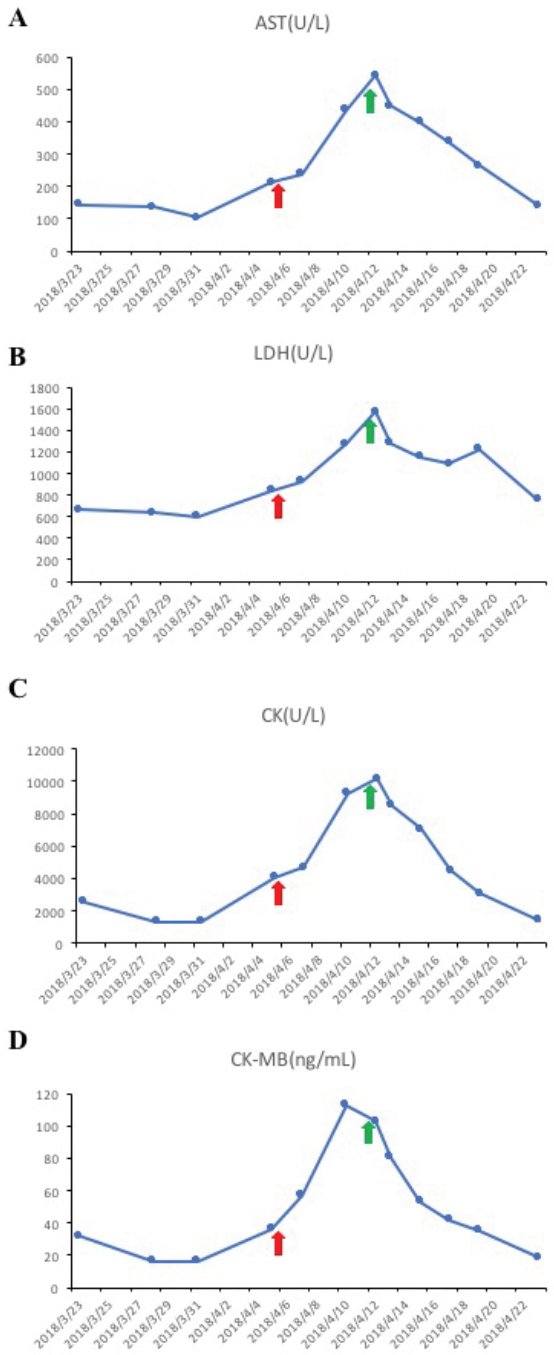

Figure 5: Changes of serum muscular enzymes during treatment. A. The changes of aspartate aminotransferase. B. The changes of lactate dehydrogenase. C. The changes of serum creatine kinase. D. The changes of creatine kinase isoenzyme. AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; CK-MB: creatine kinase isoenzyme. Red arrow indicates the time of the increase of steroid; green arrow indicates the start time of DFPP.

a plasma separator to remove pathogenic plasma or selectively remove certain virulence factors from plasma. Then, the cell components, the purified plasma, and the replenished replacement fluid are returned to the patient, thereby elimination of autoantibodies, immune complexes, cytokines, and other pathogenic factors in the circulation [7]. Double filtration plasmapheresis (DFPP) is a secondary separation of plasma from primary separation through a plasma fraction separator, the component separator performs secondary separation, and its main advantages compared to plasma exchange are: 1) selective removal of macromolecular pathogenic antibodies and immune complexes; 2) reduce the loss of nutrients; 3) reduce the amount of replacement fluid; 4) useless blood plasma [7]. However, DFPP also has some disadvantages, such as loss of albumin and fibrinogen, which may cause hypotension and bleeding. Leukapheresis is another apheresis technique for eliminating pathogenic leukocytes from circulation [8]. All of them are belong to apheresis. TPE contains plasma exchange (PE) and DFPP, which mainly removes pathogenic substances in the plasma. Leukapheresis directly removes pathogenic leukocytes, including lymphocytes, monocytes and granulocytes.

However, the effect of plasma exchange used in DM is controversial. In 1980, the first case of plasma exchange for DM in children was reported [9]. In 1988, Clarke, et al. [10] reported that plasma exchange was effective in 3 patients with DM or PM. A retrospective multicenter study showed TPE improved muscle forces in 63% patients who were resistant to conventional therapy. TPE seemed to be more effective in acute and progressive patients than in chronic and insidious patients [11]. However, in a randomized controlled trial, TPE and leukapheresis had no significant effect on improving muscle strength and function despite a decrease in serum muscle enzyme levels compared with the control group [12]. In 2015, a systematic review found plasmapheresis and leukapheresis have no beneficial effects for DM, while immunosuppressive agents could improve the clinical outcomes of DM [4]. The 2016 guidelines from the American Society for Apheresis (ASFA) (seventh edition) mentions that although TPE was seemed to be effective in some cases, it is not clearly demonstrated that TPE was responsible for the remission. There are still some cases reported that TPE has no effect on clinical symptoms [13]. Isoda, et al. [14] reported TPE plus high-dose immunosuppressants could not rescue an old woman patient who was diagnosed as DM with interstitial pneumonia complicated by chylothorax. The "2010 Guidelines for the Diagnosis and Treatment of Polymyositis and Dermatomyositis" issued by the Chinese Medical Association Rheumatology Branch also mentioned that plasma exchange has no significant effect on PM/DM treatment. However, there are still some reports that patients with DM or PM benefit from TPE. Recently, some researchers reported that three patients with PM/DM were treated with TPE after the application of glucocorticoids and immunosuppressive agents were effective. The muscle enzymes decreased significantly in a few months, the muscle strength recovered substantially, and finally reached complete remission [15]. DFPP plus IVIG rescued a severe corticosteroid-resistant DM patient with rhabdomyolysis and paralytic ileus [16]. Another research recently reported the use of extracorporeal membrane oxygenation (ECMO) combined with DFPP in the treatment of amyopathic dermatomyositis with severe interstitial lung disease, bilateral lung interstitial infiltration resorbed after treatment, the lung compliance improved and clinical symptoms ameliorated [17]. In 2012, a case report presented an acute DM male acquired quick clinical improvements after TPE when he had no responsive to traditional immunosuppressive therapies [18]. Kaieda, et al. [19] reported a DM patient with macrophage activation syndrome was rescued by combination of tacrolimus and TPE when resistant to steroid.

This patient has typical skin rash, symmetric proximal muscle weakness, elevation of muscle enzyme levels and abnormal EMG results, which can be diagnosed as DM according to Bohan and Peter's diagnostic criteria. After the treatment with glucocorticoids and IVIG, the clinical manifestations of the patient didnot improve significantly, and even the dysphagia was progressively aggravated, and the muscle enzymes continued to rise. IVIG has been proved to be beneficial for the refractory myositis [5]. However, in this case, the patient showed no responsive to IVIG. At the same time, during the treatment, the patient also developed a cough, phlegm, sputum not easy to cough up, and pneumonia is aggravated. Since the infections in the lung, other immunosuppressant agents have not been applied on this patient. Therefore, in the critical situation where the standard administration of antibiotics, steroids and IVIG has no apparent effect, and the patient's condition is exacerbated, we have adopted DFPP. After six sessions of DFPP, the symptoms of rash, muscle strength, dysphagia, and other symptoms were significantly improved, serum muscle enzymes level were significantly decreased, and infections were well controlled. This also confirms that DFPP can be used as a "rescuing" treatment for the acute phase of DM to prevent severe complications.

In conclusion, despite there is not a large body of evidence demonstrated the efficacy of TPE in the treatment of DM/PM, DFPP selectively removes macromolecular substances such as immune complexes and cytokines in plasma, when conventional steroids and immunosuppressive agents are in effective. DFPP can be used as a "rescuing" treatment option. More evidence-based medicines are still needed to confirm the efficacy of DFPP in the treatment of acute phase of steroid-resistant DM/PM.

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Ethics Approval and Consent to Participate

Written and informed consent was obtained from patient for gluococorticoids treated, double filtration plasmapheresis and for the publication of this case report, the study was carried out following the ethical principles of the Declaration of Helsinki, and was approved by the local ethical committees.

Disclosure Statement

The authors have no conflicts of interest to declare. The results presented in this paper have not been published previously in whole or in part.

Author Contribution

F.H., Y.W., I.A. and X.S. involved in conception and design of the paper; F.H., I.A., D.Z. and X.S. analysed data; D.Z. J.Z. and Y.Z. prepared figures; F.H., I.A. and Y.W. drafted the manuscript; Y.W. approved the final version of the manuscript.

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