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Successful treatment of two patients with refractory anti-MDA5-positive dermatomyositis complicated by rapidly progressing interstitial pulmonary disease: A case report

Wang QH *et al*. Two cases of MDA5+-DM-RP-ILD

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Abstract

BACKGROUND

Anti-melanoma differentiation-associated gene 5-positive (MDA5$^+$) dermatomyositis complicated with rapidly progressive interstitial lung disease (MDA5$^+$-DM-RP-ILD) has an unclear underlying mechanism with no recommended unified treatment plan. Herein, one of the cases we report (Case 2) is successfully treated by tocilizumab despite having lung infection.

CASE SUMMARY

Case 1 was a 30-year-old female who was admitted due to recurrent rash for 5 mo, fever and cough for 1 mo, and chest tightness for 3 days. She was diagnosed with non-myopathic dermatomyositis (MDA5$^+$) and interstitial pneumonia, and was treated by combination of hormone therapy and cyclophosphamide followed by oral tacrolimus. Case 2 was a 31-year-old man admitted due to systemic rash accompanied by muscle weakness of limbs for more than 1 mo, chest tightness and dry cough for 4 days. He was diagnosed with dermatomyositis (MDA5$^+$) and acute interstitial pneumonia with pneumocystis jirovecii and Aspergillus fumigatus and was treated by hormone therapy

(without cyclophosphamide) and combination of tocilizumab and tacrolimus therapy. The condition of both patients eventually improved and they were discharged and showed clinically stable condition at the latest follow-up.

CONCLUSION

Tocilizumab could be a salvage treatment for patients with MDA5$^+$-DM-RP-ILD who are refractory to intensive immunosuppression.

Key Words: Melanoma differentiation-associated gene 5-positive; Dermatomyositis; Progressive interstitial lung disease; Interstitial lung disease; Tocilizumab; Case report

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Core Tip: The early detection of myositis-related antibody profile and its concentration together with serum ferritin and cytokine levels are key elements in clinical diagnosis and prognosis of anti-melanoma differentiation-associated gene 5-positive dermatomyositis complicated with rapidly progressive interstitial lung disease (MDA5+-DM-RP-ILD). For patients of MDA5+-DM-RP-ILD refractory to intensive immunosuppression, tocilizumab could be a salvage treatment.

INTRODUCTION

At present, no consensus has been reached on the optimal treatment plan for patients with anti-melanoma differentiation-associated gene 5-positive (MDA5$^+$) dermatomyositis complicated with rapidly progressive interstitial lung disease (ILD) (MDA5$^+$-DM-RP-ILD), including on the dosage, course and reduction plan of glucocorticoids that might be used for the treatment. Due to the severity and rapid progress of the disease, it is common to adopt a large dose of hormone therapy or even

hormonal shock therapy in the early stage of the disease(1), but recent reports suggest that although high-dose hormone monotherapy may temporarily improve the general symptoms and oxygenation index of patients, it is usually ineffective in improving the prognosis of rapidly progressive interstitial lung disease (RP-ILD)(1,2), where there is also a significant risk of opportunistic infections, gastrointestinal bleeding and even death. Therefore, moderate immunosuppressive therapy and intensive supportive therapy are preferred over hormonal shock therapy.

For the treatment of anti-MDA5 antibody positive clinically amyopathic dermatomyositis (CADM) complicated with RP-ILD, the most common regimen is the so-called three-drug combination regimen of high-dose hormone, calcineurin inhibitor and intravenous cyclophosphamide; nevertheless, only a few observational studies have been conducted for this regimen (2,3). The use of other immunosuppressants such as azathioprine and mycophenolate mofetil in CADM patients with ILD is mainly based on small-scale retrospective studies and case reports, which have used them as second-line therapy (4). Methotrexate is not generally recommended to treat this disease and is associated with the risk of drug-induced hypersensitivity pneumonia. In recent years, rituximab has been proven to improve muscle strength in refractory myositis (1), but the number of clinical studies on the use of this drug for the treatment of interstitial lung lesions is low, where it should also be used with caution when there is evidence of pulmonary infection (1). Among other emerging options, one can point out combination of multiple treatment methods with direct hemoperfusion of polymyxin B (5). Report of refractory cases of MDA5^{+}-DM-RP-ILD from China is uncommon. Here, we report two cases of refractory MDA5-positive CADM presented by RP-ILD in our hospital from 2018 to 2021.

CASE PRESENTATION

Chief complaints

CASE 1: A 30-year-old female designer was admitted to the hospital due to recurrent rash for 5 mo, fever and cough for 1 mo, and chest tightness for 3 days.

CASE 2: Case 2 was a 31-year-old man admitted for systemic rash accompanied by muscle weakness of limbs for more than 1 mo, chest tightness and dry cough for 4 days.

History of present illness

CASE 1: The patient was previously treated with methylprednisolone 40 mg BID plus cyclophosphamide 0.8 qM for 3 wk at a local hospital one month ago, but her condition did not improve; she was transferred to our hospital complaining of acute chest tightness and aggravation.

CASE 2: One month before the patient's admission, fatigue appeared. Chest tightness and dry cough occurred 4 days ago, and he was hospitalized in another hospital. Next-generation sequencing (NGS) of bronchoalveolar lavage fluid suggested pneumocystis and aspergillus fumigatus. The myositis panel results were Anti-MDA5 antibody IgG+++ and anti-ro-52 (+). Methylprednisolone 80 mg and cyclophosphamide 0.8 mg IV drops were given for 10 days. Given that chest CT imaging indicated a significant increase in interstitial changes in both lungs (Fig2. 2a, 2b), he was transferred to our hospital for further diagnosis and treatment.

Physical examination

CASE 1: Multiple red skin rashes on the face (frontal, suborbital), anterior chest, bilateral elbows, interphalangeal joints, and metacarpophalangeal joints were observed, where no joint tenderness, deformity, or edema of lower limbs was identified. The patient's limbs exhibited grade IV muscle strength, and the muscle tone was normal.

CASE 2: Examination showed difficulty in raising hands and slight difficulty in raising head, and the patient had limb pain; these were accompanied with purple red rash on upper eyelid, nose root, knuckles of both palms and extension of both elbows. Physical examination suggested no superficial lymph node enlargement. A red rash could be seen on the nose, while the Gottron sign was observed on the elbow. The shoulder joint was tender with limited movement; the limbs exhibited grade V muscle strength and normal muscle tone.

Laboratory examinations

CASE 1: Blood examinations were performed after admission for the white blood cell count (6.7×10^9 /L), hemoglobin (118 g/L), platelet count (213×10^9 /L), C-reactive protein (8.0 mg/L), immunoglobulin G (26.60 g/L), immunoglobulin A (2.97 g/L), immunoglobulin M (3.85 g/L), ferritin (1455.60 µg/L), creatine kinase-MB (27 U/L), aspartate aminotransferase (1207 U/L), lactate dehydrogenase (387 U/L), and alanine aminotransferase (226 U/L).

CASE 2: The blood results were as follows: white blood cell = 15.5×10^9 /L, hemoglobin = 124 g/L, platelet count = 319×10^9 /L, sedimentation rate = 35.00 mm/h, hypersensitive C-reactive protein = 7.16 mg/L, IL-6 = 305.8 pg/mL and serum ferritin 3351 = µg/L, erythrocyte creatine kinase-MB = 1553 U/L, and lactate dehydrogenase = 699 U/L. The myositis spectrum was MDA5(+++), where electromyography suggested the presence of myogenic changes.

Imaging examinations

CASE 1: The chest CT scan showed interstitial changes in both lungs, mainly in the lower lobes (Fig1. 1b, 2b). Lung function was moderately restrictive ventilatory dysfunction and the pulmonary diffusing capacity was severely reduced.

FINAL DIAGNOSIS

CASE 1: The myositis panel results were MDA5 positive (+++) and anti-Ro-52 IgG positive (++), which led to the diagnosis of non-myopathic dermatomyositis (MDA5 positive), and interstitial pneumonia.

CASE 2: The final diagnosis was dermatomyositis ($MDA5^+$) and acute interstitial pneumonia with pneumocystis jirovecii and aspergillus fumigatus.

TREATMENT

CASE 1: After admission, the patient was notified of severe onset of acute disease, was monitored by ECG and was given oxygen. Methylprednisolone 80 mg BID was given to relieve inflammation for 1 wk, and gamma globulin 20 g QD was given for 5 days. Methylprednisolone dosage was reduced to 80 mg QD for a week and then was tapered to 60 mg QD for 7 days, with intermittent use of plasma, albumin and other symptomatic treatment to improve the body's immune function. After excluding contraindications, immunotherapy with cyclophosphamide 0.8 g once a month was provided. During hospitalization, the patient also experienced dysphagia, subcutaneous emphysema, nausea, and vomiting. After 3 wk of treatment, her condition improved, with less facial periorbital rash, cough and sputum, and no chest tightness and acute breath. The serum ferritin was 733.90 μg/L, and the patient was discharged with 50 mg prednisone QD. She was followed up for 2 years, and prednisone was tapered to 2 tablets gradually. Cyclophosphamide was changed from an intravenous drip of 0.8 g once a month for 6 mo to tacrolimus 1 mg BID. After discharge, the patient was followed up on a 2-3 mo basis.

CASE 2: Immediately after admission, the patient underwent ECG monitoring, oxygen inhalation, and nasogastric tube feeding. The treatment regimen consisted of methylprednisolone 80 mg per day followed by an additional intravenous drip twice a day to treat the primary disease, human blood gamma globulin 20 g for 5 days, intermittent support with albumin and plasma reinforcement therapy, and oral tacrolimus was adjusted to 1 mg twice a day or once a day according to the blood concentration levels. The patient experienced high fever, dysphagia, sore throat, hoarseness, and irritative cough. For alveolar lavage NGS tip's pneumocystis, SMZco, voriconazole and tocilizumab 480 mg once a month were added. The lung condition and liver injury were gradually alleviated. The repeated CRP was normal, the serum ferritin decreased to 1980 μg/L, CK index was normal (its value decreased from pre-treatment 1553 U/L to post-treatment 203 U/L) and the lung was substantially improved after repeated CT (Fig2. 3a, 3b). It should be added hormone shock was contraindicated, because this patient had obvious concurrent infection.

OUTCOME AND FOLLOW-UP

CASE 1: At the latest follow-up, the condition of the patient was stable.

CASE 2: Outpatient clinic has been followed up until now; patient's condition is stable, and chest tightness and cough are relieved (see Figure 3 for the specific drugs used by the patient).

DISCUSSION

Idiopathic inflammatory myopathy (IIM) is a group of autoimmune myopathies with etiology not fully understood. MDA5 antibody is a myositis-specific antibody relatively common in CADM subtype in IIM. In CADM, muscle involvement is mostly mild. RP-ILD is highly correlated with CADM with an incidence of 24%~65%, which often leads to respiratory failure(6). Half of patients with respiratory failure die due to respiratory failure progression, where the survival time between the appearance of respiratory symptoms and death is only 2 to 3 mo under the therapeutic effect of treatment using immunosuppressants(6).

The main clinical manifestations of anti-MDA-5 antibody-positive CADM are rash, joint muscle soreness, muscle weakness, hoarseness, choking, mediastinal emphysema, and rapidly progressive ILD. It has been established that anti-MDA-5 antibody-positive CADM with RP-ILD progresses rapidly and is more difficult to treat than classic dermatomyositis complicated with rapidly progressive interstitial lung disease (DM-ILD)(6). The acute disease onset in half of CADM patients may be accounted for by the overactivation of alveolar macrophages, leading to neutrophil activation, release of lymphocyte chemokines, pathological inflammation and, ultimately, lung tissue damage. It has been reported that approximately 50% of clinically amyopathic dermatomyositis with rapidly progressive interstitial lung disease patients die during the early disease stages(7,8). Studies on adverse factors suggest that ferritin and interleukin-18 in DM-ILD patients with positive anti-MDA5 antibodies are significantly increased and are positively correlated with disease activity(9,10). The fact that for our two patients

serum ferritin decreased substantially after treatment suggests that a positive correlation exists between serum ferritin and disease activity.

Muro *et al* documented that the serum anti-MDA5 antibody level of 11 newly treated CADM patients with ILD decreased after treatment and even turned negative in some cases, suggesting that anti-MDA5 antibody can be used to evaluate the efficacy of treatment in RP-ILD patients(11). Gan *et al* proposed that cellular keratin 19 fragment (CyFRA21-1) is also a risk factor and a useful marker for detecting rapidly progressive ILD caused by MDA5-resistant CADM(12). Huang *et al* found that the incidence of subcutaneous emphysema, hoarseness and dysphagia in patients with positive anti-MDA5 and anti-RO52 antibodies was significantly higher than those in patients with only positive anti-MDA5 antibodies; also the mortality rate of the former patients was as high as 54.55%(13). These findings suggest that the early detection of myositis-related antibody profile and its concentration together with serum ferritin and cytokine levels are key elements in clinical diagnosis and prognosis.

For the two cases of severely-ill patients successfully treated in our hospital, no large dose of hormonal shock therapy was applied; at the start of the treatment methylprednisolone was used at 80 mg (intravenous administration), which was later gradually reduced to oral treatment. Infection is one of the important causes of death in such patients, especially those treated with high-dose hormone combined with multiple immunosuppressants. Thus, it is essential that the patients are provided with supportive treatment, such as intermittent infusion of plasma and albumin, and attention should be paid to their 24-hour intake of water and their electrolyte balance. In addition, there is no clear treatment guideline for immunosuppressants.

For treating one of the cases reported here (Case 1), combination of hormone therapy and cyclophosphamide was used, which after half a year was changed to oral tacrolimus. For the other patient (Case 2), due to the accompanying pulmonary fungal infection, hormone therapy was not combined with cyclophosphamide; instead, the combination of tocilizumab and tacrolimus therapy was used to address the primary disease. The patients' condition eventually improved and they were discharged. At the

latest follow-up, the patients were found to be clinically stable. Thus, the relatively satisfactory outcome of treatment with tocilizumab in Case 2 may indicate that tocilizumab could be a salvage treatment for patients with RP-ILD who are refractory to intensive immunosuppression. To our knowledge, there is only one prior report of using tocilizumab for treatment of dermatomyositis, where tocilizumab was found to be effective for the treatment of six patients(14). With respect to targeting other cytokines, such as tumor necrosis factor-alpha (TNF-a) and type 1 interferon (T1-IFN), we should point out the following. First, examining data of 122 cases of new-onset or exacerbation of ILD secondary to administration of biologic therapies revealed that in 97% of cases the biologic agent used was blocking TNF-a(15), which discouraged us from considering targeting TNF-a in our patients. With respect to the significance of type 1 interferon (T1-IFN) in the pathogenesis and treatment of MDA5+-DM-RP-ILD we should say that high T1-IFN signatures in serum and affected skin of MDA5+-DM-RP-ILD patients have been reported highlighting the potential of targeting T1-IFN as a treatment strategy in such patients(16). Nevertheless, we are unaware of a report in the literature that has tested this treatment strategy in patients with MDA5+-DM-RP-ILD. In this context, we should point out that a Phase I b randomized, double-blind, controlled clinical study of sifalimumab found elevated T1-IFN gene signaling in 77% of patients with inflammatory myopathy(17). Sifalimumab is currently not marketed in China and its efficacy in treating polymyositis/dermatomyositis-related pulmonary interstitial lesions remains to be observed. Thus, due to the very high mortality of MDA5+-DM-RP-ILD and the circumstances around targeting TNF-a and T1-IFN, our decision to use tocilizumab was based on the above-mentioned prior report(14) and also the fact that IL-6 is closely related to the pathogenesis of MDA5+-DM-RP-ILD(18). Given that for patients with serious lung infections the combination of other biological agents and immunosuppressants are contraindicated, the relatively satisfactory outcome observed in Case 2 for tocilizumab is noteworthy. Of course, further follow-up is needed to clarify this potentially meaningful treatment.

CONCLUSION

In conclusion, the prognosis of RP-ILD in patients with anti-MDA5-positive dermatomyositis is poor, and the fatality rate is high for such patients. The underlying mechanism of this disease remains poorly understood, and no consensus has been reached on the optimal treatment plan. Early detection of myositis-related antibody spectrum, its concentration, and levels of serum ferritin and cytokines are key for clinical diagnosis and prognosis assessment of this disease. For patients with high titers of anti-MDA5 antibodies, high serum ferritin, or adverse prognostic factors clinicians should adopt more aggressive treatment regimens to improve patient survival rate. In addition to symptomatic therapy, the three-drug combination therapy scheme consisting of high doses of glucocorticoids, calcineurin inhibitors and intravenous cyclophosphamide is recommended; tocilizumab represents a potential solution for enhancing the immune suppression of rescue medications in patients with refractory of RP-ILD. Larger clinical studies are warranted to corroborate our findings.

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Figure Legends

Figure 1 Computed tomography (CT) findings of Case 1. (Left images 1a, 2a) Patchy exudation and interstitial changes were observed in both lungs on admission. (Right images 1b, 2b). After 4 wk of hormone and cyclophosphamide treatment, only mild subpleural gridded changes were observed in both lungs.

Figure 2 Computed tomography (CT) findings of Case 2. (1a, 1b) Scattered flaked ground-glass shadows in both lungs and multiple cords in the lower lungs on admission were observed; (2a, 2b) multiple patchy subpleural exudation, consolidation and interstitial changes were observed in both lungs; also, multiple infectious legions were noted, which were noticeably worse than before; (3a, 3b) subpleural exudation and consolidation were observed to a large extent after hormone therapy in combination with tocilizumab treatment.

Figure 3 Regimen adopted for the treatment of Case 2. IVIG: intravenous gamma globulin; mPSL: methylprednisolone; Tac：tacrolimus; Oxy: oxygenation support

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