Case Report: Successful treatment of anti-MDA5-positive to negative dermatomyositis-associated interstitial lung disease with the JAK inhibitor tofacitinib

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Abstract

Anti-MDA5 antibody-positive dermatomyositis (DM) is a rare clinical autoimmune disease, and anti-MDA5-positive DM with interstitial lung disease (ILD) is the most important cause of death in DM patients. We reported the efficacy of the JAK1/3 inhibitor tofacitinib as an anti-MDT5-negative treatment option for patients with anti-MDA5-positive DM-ILD. Here we report a 51-year-old female patient with cough, sputum, shortness of breath for 5 months, rash for 3 months, and muscle pain in the extremities for 1 month. After conventional immunosuppressive therapy plus hormone therapy, the remission was slow. Methylprednisolone was successfully reduced after we administered tofacitinib and tacrolimus. After 132 weeks of follow-up, anti-MDA5 antibody turned negative, clinical symptoms were relieved, and lung Imaging tests were successfully reversed. There is currently no report of tofacitinib supplement therapy for anti-MDA5 positive to negtive DM. With this case report, tofacitinib is an option for the treatment of anti-MDA5-positive DM-ILD, which deserves attention.

Introduction

Dermatomyositis(DM) is an autoimmune disease with clinical manifestations of muscle and skin damage, often accompanied by multisystem involvement, especially in the lungs(Didona et al., 2020). Positive anti-MDA5 antibodies are highly associated with interstitial lung disease (ILD), which is a major mortality factor in patients(Bai et al., 2021). Current conventional drug treatments for DM-ILD include glucocorticoids, immunosuppressants, and anti-pulmonary fibrosis drugs(Waldman et al., 2020). Long-term use of glucocorticoids can lead to many adverse reactions, a high risk of immunosuppressive infections, unpredictable adverse drug reactions, and the duration of treatment with anti-pulmonary fibrosis drugs is difficult to manage, resulting in DM-ILD patients, especially those with positive anti-MDA5 antibodies. However, the effective treatment rate is low. As a small-molecule targeted drug, many studies have confirmed the effectiveness of tofacitinib in the treatment of patients with anti-MDA5-positive DM-ILD(Chen et al., 2019, Ding et al., 2021). However, there are no reports of negative conversion of anti-MDA5 antibodies to tofacitinib treatment. Here, we report a case of anti-MDA5 antibody-positive DM-ILD in a patient who was treated with hormones and immunosuppressive agents in combination with tofacitinib and had negative anti-MDA5 antibodies, which are summarized below for clinical reference.

CASE REPORT

A 51-year-old female patient with a 10-year history of psoriatic arthritis developed paroxysmal cough and cough with white, sticky sputum after a cold 5 months ago, accompanied by chills, general malaise, chest tightness, shortness of breath, back pain, and hoarseness after exercise. She did not improve after cold treatment. Two months later, shortness of breath after activity and speech worsened, and there was scattered erythema on the neck, some of which merged into a piece, rough skin on the radial side of the right index

finger, the distal end of the hands, and white skin after cold; a chest CT was performed at an external hospital. Interstitial infection in the right lobe, lingual segment of the upper lobe of the left lung, and lower lobes of both lungs was observed, and electronic bronchoscopy showed no abnormalities. Pulmonary function tests revealed moderate restrictive ventilatory dysfunction, small airway dysfunction, and moderate diffusion impairment. Electromyography revealed a trend toward myogenic injury in the proximal muscles of the extremities. Bilateral interstitial pneumonia and connective tissue disease were also considered. To combat the infection, methylprednisolone 40 mg once daily and pirfenidone 200 mg three times daily were used for treatment, and the cough and sputum improved, with no improvement in shortness of breath after exercise, without further deterioration. After four months of activity, chest tightness, shortness of breath, cough, and white sputum appeared. She went to the Department of Respiratory Medicine, West China Hospital, Sichuan University, for examination of anti-Mi-2α, anti-MDA5, and anti-PM Scl antibodies (+-). CT scan of the Chest computed tomography revealed vitreous opacities, patchy shadows, and grid-like shadows in both lung membranes, mostly due to interstitial inflammation in both lungs. Biopsy of the left deltoid muscle dermatomyositis skeletal myopathy could not be excluded, followed by methylprednisolone modulation of immunity and no significant relief of symptoms after anti-infection therapy. We considered that our department should check for positive anti-MDA5 antibodies to diagnose DM and to check the finger pulse. Oxygen 89% (no oxygen inhalation), dry and wet rales could be heard, a small amount scattered in the lower lungs, veclro rales could be heard in the bases of both lungs, chest CT showed chronic interstitial changes in both lungs; mixed type in the lower lobes of both lungs Possibility of infection, fungus, procalcitonin**(Figure 1)** , C-reactive protein, erythrocyte sedimentation rate, muscle enzyme spectrum, electrolytes, thyroid function, tumor markers were normal, excluding other autoimmune diseases and tumors, sputum culture was Lewy persistent bacillus infection, antibiotic anti-infective treatment and methylprednisolone 40 mg qd (reduced by 4 mg per week), cyclosporine 25 mg bid, pirfenidone 200 mg tid treatment, cough, sputum, chest tightness, shortness of breath, muscle pain significantly improved, no skin damage.

After 12 weeks of treatment, the patient visited Peking Union Medical College Hospital and was found to be anti-MDA5 positive. The patient was treated with methylprednisolone (12 mg qd), tacrolimus (2 mg qd), cyclophosphamide (50 mg qd), and pirfenidone (200 mg). No rash was observed after treatment. Muscle pain was present, but chest tightness, shortness of breath, cough, and sputum production were observed.

After 36 weeks of treatment, considering the toxic side effects of cyclophosphamide, after excluding infection, tumor, tuberculosis, and hepatitis, we adjusted the treatment plan to methylprednisolone 6 mg qd, tacrolimus 2 mg qd, tofacitinib 5 mg bid, and pirfenidone 200 mg tid. Chest tightness and shortness of breath, cough, and expectoration continued to be relieved, and hormone levels were successfully reduced after 52 weeks of treatment. Tacrolimus Capsules 1 mg qd remained in remission and underwent multiple follow-ups; the anti-MDA5 antibody was positive many times using the Cytometric Bead Array (CBA) detection method.

At the 132 weeks of follow-up, we comprehensively evaluated the patient's condition. Pulse oxygen was 95% (without oxygenation), and pulmonary function was normal. After repeated checks, the anti-MDA5 antibody was negative, and the symptoms continued to be relieved. First, we continued to administer tacrolimus division 1 mg qd, tofacitinib 5 mg bid, and pirfenidone 200 mg qd maintenance therapy (**Figure 2)** . It is worth noting that the patient's muscle enzyme, immunoglobulin, C-reactive protein, and erythrocyte sedimentation rates were normal from the onset to the 132-week follow-up(**Figure 3)** .

DISCUSSION

Anti-MAD5 antibody-positive DM has a rapid onset, more severe disease, and worse prognosis. ILD is the leading cause of death in patients with anti-MDA5 antibody-positive DM patients(Motegi et al., 2019, Yamaoka et al., 2014). DM is a rare disease, and many drugs have been recommended for its treatment, including glucocorticoids, methotrexate, tacrolimus, cyclosporine, and intravenous immunoglobulin, which have been proven to be clinically effective(Lundberg et al., 2017). However, when the abovementioned adverse reactions occur or are ineffective, there are few drugs to choose from. Tofacitinib has been shown to have good efficacy in patients with DM patients(Paik et al., 2021, Kurasawa et al., 2018). On this basis, we selected tofacitinib with the full informed consent of the patients and achieved a good curative effect.

Reviewing this patient, although serum muscle enzymes were not elevated throughout, our diagnosis was considered despite the consistent absence of elevated serum myosin and the presence of fatigue, neck rash, electromyography suggestive of myogenic lesions, muscle biopsy suggesting inflammatory myopathy, changes in ILD, and positive myositis antibody and anti-MDA5 antibody. Anti-MDA5 antibody was positive for DM. Initially, the patient responded well to treatment, but as the steroids were tapered, the patient's symptoms and imaging findings did not resolve significantly. The patient did not experience significant relief even with the addition of cyclophosphamide and tacrolimus. However, we attempted tofacitinib because of the prolonged use of tacrolimus and the negative effects of steroid hormones, and we were able to successfully reduce and cease using steroid hormones after 16 weeks of tofacitinib treatment. The anti-MDA5 antibody test was effectively negative after 96 weeks, but the patient's symptoms persisted. The remission, lung CT, and ILD manifestations were successfully reversed. Therefore, we believe that it plays a potential role in the maintenance therapy of anti-MDA5 antibody-positive DM-ILD.

In conclusion, we report a patient with anti-MDA5 antibody-positive DM-ILD and conclude for the first time that tofacitinib may be an option for anti-MDA5 antibody-positive conversion during maintenance therapy. However, further clinical and experimental studies are needed to confirm this hypothesis.

PATIENT PERSPECTIVES

Throughout the clinical course, the patients were fully informed about the treatment and potential side effects and agreed to the treatment.

DATA AVAILABILITY STATEMENT

The original contributions of the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Informed patient consent was obtained for the publication of any potentially identifiable images or data.

AUTHOR CONTRIBUTIONS

JZ actively wrote the manuscript and created the fifigures.TF provided constructive advice and critically revised the manuscript. YXL edited the manuscript. MWK guided treatment.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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