Seroconversion for Anti-melanoma differentiation-associated protein5 (Anti-MDA5)

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Summary

A sixty-six-year-old Thai female presented with progressive dyspnea and non-productive cough. She was diagnosed with MDA-5 dermatomyositis with rapidly progressive interstitial lung disease (RP-ILD) from UIP pattern in her high-resolution computed tomography-chest (HRCT-chest) and anti-MDA5 strongly positive in her myositis profile. After one year of treatment with steroid and immunosuppressive therapy, follow-up testing of anti-MDA-5 became negative in result.

Case presentation

A sixty-six-year-old Thai female with history of treated pulmonary tuberculosis 30 years ago, presented to local hospital with progressive dyspnea, non-productive cough and myalgia for one week. She denied any fever, weight loss, rash or arthritis. Physical examination revealed bilateral Velcro crackle sound both lower lungs, otherwise negative. Chest X-ray showed reticular infiltration with ground glass opacity both lower lungs (Figure 1) and sputum was negative for acid fast bacilli. Based on all the information, the patient was treated as smear negative pulmonary tuberculosis for 8 weeks. After treatment, she went to the doctor before her appointment and complaint that she was unable to do her regular job or walk long distances because her dyspnea and cough symptoms had worsened. At the same time as the sputum culture results came out, it was found that no growth of tuberculosis was observed. Due to suspicion of rapidly progressive interstitial lung disease, the patient has been scheduled for a HRCT-chest and referred to pulmonary unit at Rajavithi hospital.

Upon arrival at pulmonary unit, the patient was presented with no febrile but looked dyspnea. Her temperature was 36.7 ° C, blood pressure was 110/70 mmHg, heart rate was 110 beats per minute, respiratory rate was 30 breaths per minute and oxygen saturation was 91% on room air.

On the day of presentation, the initial laboratory test revealed that mild anemia, inflammatory markers, both ESR and high sensitivity CRP, were elevated. On the other hand, CPK was normal (Table 1). HRCT-chest revealed traction bronchiectasis at right middle and left upper lung, diffuse mild peri-bronchial wall thickening and tree in bud appearance including bronchiolitis (Figure 2). The patient underwent a bronchoscopy and blood test for myositis profile that the results showed negative for infection including tuberculosis and bacteria and strongly positive for Anti-melanoma differentiation-associated protein 5 (Anti-MDA5) respectively.

Table 1 The initial investigations

Parameters	Results
Hemoglobin (g/dL)	11.9
Hemotocrit (%)	36.8
Mean corpuscular volume (fL)	90
RBC distribution width	12.7
White blood cell count	9430
Polymorphonuclear cell (%)	68.9
Lymphocyte (%)	24.2
Monocyte (%)	5.4
Eosinophil (%)	1.2
Basophil (%)	0.3
Platelet count	348,000

BUN	13
Creatinine	0.62
ESR	81
High sensitivity-C reactive protein (<0.5 mg/L)	2.58
Total protein (g/dL) (6.6-8.7)	7.7
Albumin(g/dL) (3.5-5.2)	3.7
Globulin(g/dL)	4.0
Total bilirubin(mg/dL) (0.1-1.2)	0.29
Direct bilirubin(mg/dL) (< 0.3)	0.14
Aspartate transferase (U/L) (0-50)	10
Alanine transaminase (U/L) (0-50)	15
Alkaline phosphatate (U/L) (35-104)	13
CPK	60
Myositis profile	
Mi-2 Alpha	Negative
Mi-2 beta	Negative
TIF 1 gamma	Negative
MDA 5	Strongly positive
NXP 2	Negative
SAE 1	Negative
Ku	Negative
PM Scl-100	Negative
SAE	Negative
Bronchoalveolar lavage for AFB	Negative
Bronchoalveolar lavage gene X-pert for TB	MTB not detected
Bronchoalveolar culture for TB	No growth
HbsAg, anti-HBc, anti-HBs, anti-HCV	Negative

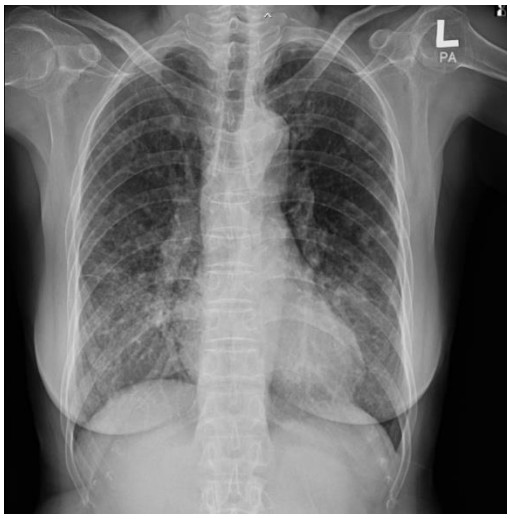

Figure 1 Chest X-ray showing ground-glass opacity and reticular infiltration predominantly in both lower lung areas.

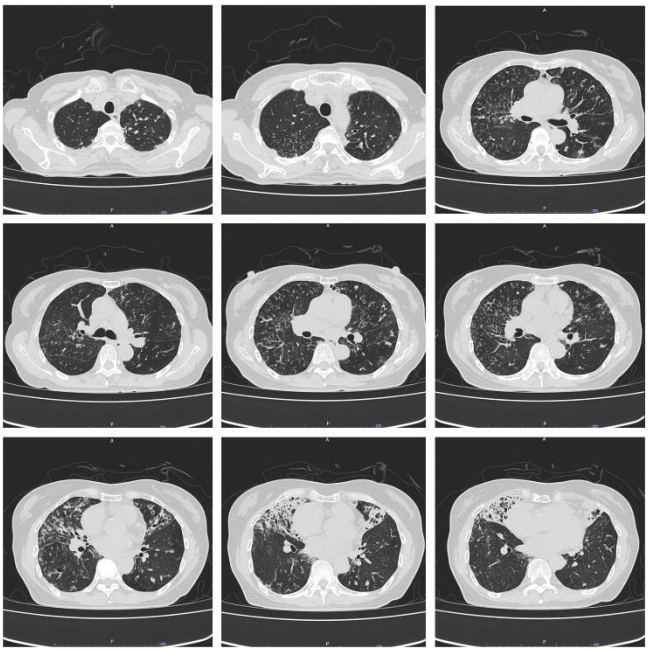

Figure 2 High-resolution computed tomography scan showing traction bronchiectasis at right middle and left upper lung, diffuse mild peri-bronchial wall thickening and tree in bud appearance including bronchiolitis.

Diagnosis

In this patient, MDA-5 dermatomyositis with RP-ILD was diagnosed from UIP pattern in HRCT-chest and anti-MDA5 strongly positive in myositis profile.

Treatment and Outcomes

After MDA-5 dermatomyositis with RP-ILD was diagnosed, she was treated with 30 mg/day of prednisolone, mycophenolate mofetil (titrated up to 2 grams/day), and 50 mg/day of cyclosporine.

Three months after treatment, the patient came to rheumatology unit out-patient for a follow-up. She complained that she had developed a painful neck mass and low-grade fever for one week. Physical examination revealed bilateral anterior cervical lymphadenopathy, approximately 4×4 cm in size, with a firm consistency and tenderness. A biopsy of the right cervical lymph node demonstrated organizing suppurative with necrotizing inflammation and the tissue culture positive for Escherichia coli. Bacterial lymphadenitis was diagnosed and treated with oral amoxicillin/clavulanic acid.

After two weeks of antibiotic treatment, the neck masses had disappeared and her dyspnea symptoms had also improved, oxygen saturation was 98% on room air; therefore–prednisolone and immunosuppressive drugs were taped down. Follow-up testing for anti-MDA-5 approximately one year after treatment was negative.

Literature review and Discussion

Anti-melanoma differentiation-associated protein 5 (MDA5) antibody positive dermatomyositis (MDA5-DM) is a distinct subtype of dermatomyositis characterized by seroreactivity to the autoantigen MDA5, skin ulceration, rapidly progressive interstitial lung disease (RP-ILD) and less or absent muscle involvement[1]. Anti-MDA5 antibodies have been reported in approximately 1%–30% patients with idiopathic inflammatory myopathy (IIM)[2].

Interstitial lung disease (ILD) is one of the most prevalent and recognizable clinical features of MDA5-DM, with a prevalence of approximately 40–100%[3]. MDA5-DM-associated RP-ILD responds poorly to currently available treatment options and is the leading cause of death in MDA5-DM[4]. However, the reported incidence of RP-ILD varies considerably across different cohorts and is notably higher in East Asian populations than in white populations[5,6,7-9]. A meta-analysis study primarily focusing on East Asian populations (including 8 studies from Japan, 3 from China, 1 from Korea and 1 from the USA) indicated that the risk ratio for RP-ILD was 20 times higher in patients with MDA5-DM than in patients with anti-MDA5 antibody-negative dermatomyositis[10].

The HRCT-chest in patients with MDA5-DM and commonly include organizing pneumonia, which typically presents with subpleural consolidation during the early stage of the disease, non-specific interstitial pneumonia and non-specific interstitial pneumonia–organizing pneumonia overlap, whereas usual interstitial pneumonia is rare[11].

In our patent, sixty-six-year-old Thai female presented with progressive dyspnea and non-productive cough. HRCT-chest revealed traction bronchiectasis compatible with usual interstitial pneumonia and Anti-MDA5 antibody positive. She was diagnosed as MDA5-DM with RP-ILD. After treatment with prednisolone, mycophenolate mofetil and cyclosporin the patient's symptoms improved. Follow-up testing for anti-MDA5 approximately one year after treatment showed anti-MDA5 negativity.

Previous studies have demonstrated that serum levels of anti-MDA5 antibodies correlate positively with disease activity in MDA5-DM[12-14]. Disease remission is associated with a decrease in anti-MDA5 antibody titers, as measured by ELISA, with antibodies even decreasing to undetectable levels in some patients; furthermore, an increase in anti-MDA5 antibodies has also been reported to predict disease relapse[13]. Anti-MDA5 antibody titers, as detected by ELISA, have also emerged as a potentially important prognostic indicator[13-16].

There is a case report form China about 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 Methylprednisolone, tofacitinib and tacrolimus for 132 weeks of follow-up, anti-MDA5 antibody turned negative, clinical symptoms were relieved, and lung Imaging tests were successfully reversed[17].

Furthermore, the value of the anti-MDA5 Antibody could also be useful for the evaluation of the response to treatment. In a Japanese cohort, patients with anti-MDA5 antibody levels greater than 500 units/mL (positivity threshold at 8 units/mL) were resistant to treatment by glucocorticoids/cyclophosphamide or intravenous immunoglobulins, and died[18]. Inversely, patients with anti-MDA5 Antibody levels lower than 500 units/mL had less severe lung lesions and cutaneous symptoms improved after treatment. Finally, monitoring the anti-MDA5 antibody levels along the course of the disease could permit to objective a remission or to detect a relapse early. Remission induces the disappearance of anti-MDA5 antibody, whereas it remains elevated in the patients who die or who later relapse[19,20].

In addition, anti-MDA5 antibody can yield false-positive result due to the following reasons; cross-reactivity with other autoantibodies such as systemic lupus erythematosus, infections such as Epstein-Bar virus, cytomegalovirus, technical issues with assays, medication-induced autoimmunity such as immune check point inhibitors, healthy individuals or subclinical disease[6-7,21].

In this patient, the anti-MDA5 antibody negativity resulted from disease improvement following steroid and immunosuppressive treatment.

Conclusion

MDA5-DM is associated with RP-ILD and can lead to fetal outcome. However, with appropriate treatment, symptoms can improve. The MDA-5 antibody can serve as a predictor and may undergo seroconversion when the disease improves.

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