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Clinical characteristics of anti-MDA5 antibody-positive interstitial lung disease

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Abstract

Clinically amyopathic dermatomyositis (CADM) with anti-melanoma differentiation-associated gene 5 antibody is associated with rapidly progressive interstitial lung disease (RP-ILD) which results in up to 50% mortality, especially within six months of diagnosis. However, limited data are available on this disease. This is the first case series of six patients in Thailand diagnosed with CADM with ILD. All patients presented with respiratory symptoms, such as progressive dyspnoea, dyspnoea on exertion, or cough. High-resolution computed tomography of the chest showed predominantly subpleural and peripheral consolidation in both lower lungs. Four patients had RP-ILD and three of the RP-ILD patients died within seven weeks of diagnosis. These cases illustrate the clinical characteristics, chest imaging, treatments, and clinical outcomes of the patients diagnosed with CADM and ILD.

Introduction

Clinically amyopathic dermatomyositis (CADM) is a subtype of dermatomyositis (DM) which presents as classical skin manifestations without muscle weakness or elevated muscle enzyme levels [1]. Anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody has been identified as an associated factor in rapidly progressive interstitial lung disease (RP-ILD). RP-ILD is associated with a 50% mortality rate in patients with CADM, especially within six months of diagnosis [2,3]. We report six Thai patients diagnosed with anti-MDA5 antibody-positive ILD (Table 1). Four patients had anti-MDA5 antibody-positive RP-ILD.

Case Series

Case 1

A 45-year-old man, ex-smoker, presented with one month of productive cough, dyspnoea on exertion, and low-grade fever. Physical examination showed heliotrope rash, V-sign, photosensitive rash, and mechanic's hands. Lung auscultation revealed coarse crepitation in both lower lungs. A chest X-ray (CXR) revealed ground-glass opacities (GGO) and high-resolution computed tomography (HRCT) of the chest showed subpleural and peripheral consolidation in both lower lungs (Fig. 1A). A transbronchial biopsy showed changes of organizing pneumonitis. He developed acute respiratory failure and was intubated within three days of admission. A subsequent CXR revealed bilateral patchy infiltration in both middle and lower lungs. His condition deteriorated despite intravenous dexamethasone and methylprednisolone pulse therapies, and he had persistent hypoxaemia despite a high setting on mechanical ventilation. His serum ferritin increased from 2360 to 6872 ng/mL. He died nine days into his admission. The anti-MDA5 antibody test was later reported as positive and a lung necropsy reported diffuse alveolar damage.

Case 2

A 35-year-old woman, non-smoker, presented with four months of acute symmetrical polyarthritis. She was previously diagnosed with systemic lupus erythematosus due to the presence of antinuclear antibodies with a homogeneous

Table 1. Clinical characteristics of anti-MDA5 antibody-positive ILD.

Case number	1	2	3	4	5	6
Gender	Male	Female	Female	Male	Male	Female
Age	45	35	58	63	49	58
Smoking history	Ex-smoker (13 pack-years)	Non-smoker	Non-smoker	Ex-smoker (40 pack-years)	Non-smoker	Non-smoker
Comorbidities	—	Subacute thyroiditis	HT, DLP	COPD	HT, DLP	Asthma
Onset of symptoms	One week	One month	Two weeks	Three weeks	Three months	Two months
Respiratory symptoms	Dyspnoea on exertion, cough, weight loss	Dyspnoea on exertion, cough	Progressive dyspnoea	Progressive dyspnoea, dyspnoea on exertion, cough	Productive cough, progressive dyspnoea	Chronic cough
Laboratory investigation						
Ferritin (ng/mL)						
Initial diagnosis	2360	1102	2129	901	1944	335
After treatment	6872	1328	112	409	578	210
CPK (U/L)	404	282	482	187	—	52
Aldolase (U/L)	17.9	17.9	12.2	—	—	15.5
hs-CRP (mg/L)	107.88	21.67	—	6.02	0.91	—
LDH (U/L)	689	1023	922	743	—	565
ANA	1:80	1:640	Negative	Negative	Negative	1:80
Anti-myositis profile						
Anti-MDA5 antibody	Positive	Strongly positive	Positive	Strongly positive	Positive	Positive
Anti-Ro52 antibody	Positive	Strongly positive	Negative	Positive	Negative	Negative
Anti Mi-2 beta	Negative	Positive	Borderline	Negative	Negative	Borderline
Pulmonary function test (initial diagnosis)						
FVC (% predicted)	NA	NA	NA	NA	62	58
TLC (% predicted)	NA	NA	NA	NA	79	64
DLCO (% predicted)	NA	NA	NA	NA	72	45

Table 1. Continued

Case number	1	2	3	4	5	6
Pathological findings	Organizing pneumonitis	Patchy interstitial fibrosis with focal organizing pattern	Bronchiolitis obliterans organizing pneumonia	NA	NA	Chronic inflammation
Chest imaging findings	Subpleural and peripheral consolidation	Multifocal GGO and consolidations at subpleural regions	Subpleural and peribronchial GGO	Bilateral subpleural GGO	Peripheral GGO, reticulation and bronchiectasis	Nodules, GGOs and consolidation
Treatment	Dexamethasone, IVMP	IVMP, mycophenolic acid, cyclosporine, rituximab	IVMP, IVCY, cyclosporine, mycophenolic acid	Dexamethasone, IVMP, plasma exchange	Oral prednisolone, mycophenolic acid, rituximab	Oral prednisolone, mycophenolic acid, oral cyclophosphamide
RP-ILD	Yes	Yes	Yes	Yes	No	No
Disease duration, days (until 15 November 2020)	Nine	20	600	44	451	1270
Outcome	Death	Death	Alive	Death	Alive	Alive

ANA, antinuclear antibody; COPD, chronic obstructive pulmonary disease; CPK, creatine phosphokinase; DLCO, diffusing capacity of the lung for carbon monoxide; DLP, dyslipidaemia; GGO, ground-glass opacities; FVC, forced vital capacity; hs-CRP, high-sensitivity C-reactive protein; HT, hypertension, ILD, interstitial lung disease; IVCY, intravenous cyclophosphamide; IVMP, intravenous methylprednisolone; LDH, lactate dehydrogenase; MDA5, melanoma differentiation-associated gene 5; NA, not assessed; RP-ILD, rapidly progressive ILD, TLC; total lung capacity.

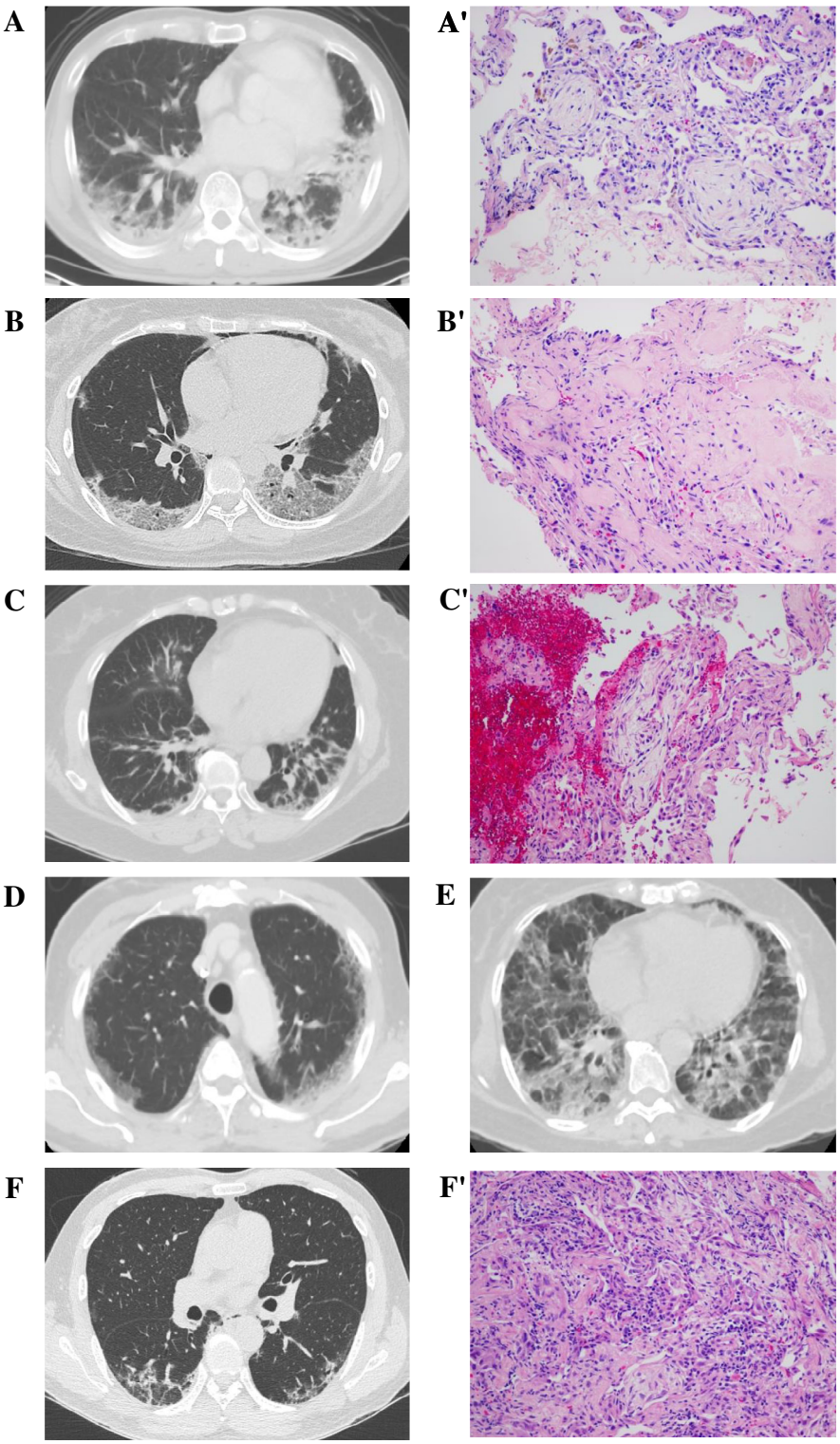

Figure 1. High-resolution computed tomography (HRCT) of chest findings and lung biopsy specimens (haematoxylin and eosin (H&E) stain, 200× magnification). (A) Subpleural and peripheral consolidation in both lower lungs, (A′) organizing pneumonitis. (B) Multiple scattered foci of mixed consolidations and ground-glass opacity (GGO) in both basal lungs, (B′) patchy interstitial fibrosis with focal organizing pattern. (C) Subpleural and peribronchial GGO in both lungs, (C′) bronchiolitis obliterans organizing pneumonia. (D) Bilateral subpleural GGO (unavailable lung biopsy). (E) GGO with some consolidations (unavailable lung biopsy). (F) Peripheral GGO, reticulations, and bronchiolectasis, (F′) chronic inflammation.

pattern (1:640 titre). Two months later, she developed a productive cough, increasing dyspnoea on exertion, and low-grade fever for one month. Physical examination showed heliotrope rash, V-sign, photosensitive rash, and mechanic's hands. Lung auscultation revealed fine crepitation in both lower lungs. A CXR revealed GGO scattered

in both lower lungs and a chest HRCT showed multiple scattered foci of mixed consolidations and GGO in both lungs (Fig. 1B). A transbronchial biopsy showed patchy interstitial fibrosis with a focal organizing pattern. Her anti-MDA5 antibody test was positive. She was diagnosed with CADM-ILD and treated with methylprednisolone pulse therapy for three days followed by mycophenolic acid and cyclosporine. Although she improved initially, she subsequently developed increased dyspnoea and hypoxaemia one week after discharge from hospital. She had bibasal coarse crepitations on chest auscultation and a partial pressure of oxygen (PaO_2) of 51.8 mmHg on arterial blood gas. A chest HRCT revealed increased multifocal bilateral GGO with consolidation, pneumomediastinum, and an enlarged pulmonary trunk of 3.3 cm in diameter. She was given methylprednisolone pulse therapy and rituximab, but did not respond to therapy. She had severe persistent hypoxaemia despite a high setting on mechanical ventilation and recruitment manoeuvres. She died 20 days into her admission.

Case 3

A 58-year-old woman, non-smoker with hypertension (HT) and dyslipidaemia (DLP), presented with one year of chronic polyarthralgia and three months of progressive dyspnoea and low-grade fever. Physical examination revealed mild tenderness at both proximal interphalangeal joints. Lung auscultation revealed fine bibasal crepitation. A CXR revealed reticular infiltration in both lungs and a chest computed tomography showed diffuse subpleural and peribronchial GGO in both lungs (Fig. 1C). A transbronchial biopsy showed changes of bronchiolitis obliterans organizing pneumonia. Her anti-MDA5 antibody test was positive. She was diagnosed with CADM-RP-ILD and treated with methylprednisolone pulse therapy and intravenous cyclophosphamide followed by oral prednisolone and cyclosporine. She improved initially but developed worsening dyspnoea and hypoxaemia two months later. A chest HRCT revealed progressive multifocal bilateral GGO with consolidation. After administration of mycophenolic acid and prednisolone 40 mg/day, her clinical symptoms and chest imaging improved. She is still alive 18 months after diagnosis.

Case 4

A 63-year-old man, ex-smoker with chronic obstructive pulmonary disease (COPD) Global Initiative for Chronic Obstructive Lung Disease (GOLD) B, presented with two months of bowel habit change and significant weight loss. He also had low-grade fever with progressive dyspnoea and dyspnoea on exertion for three weeks. His physical examination showed heliotrope rash, shawl-sign, V-sign, photosensitive rash, and mechanic's hands. Lung auscultation revealed bibasal coarse crepitation. A CXR revealed GGO in both lower lungs and an HRCT showed bilateral subpleural GGO (Fig. 1D). His anti-MDA5 antibody test was strongly positive. Intravenous dexamethasone was given. At day 9 after admission, his respiratory symptoms deteriorated. A chest HRCT revealed progressive multifocal GGO. He was diagnosed with CADM-RP-ILD and treated with methylprednisolone pulse therapy, but his symptoms did not improve. Plasma exchange was initiated because he also had strongyloidiasis. After plasma exchange was performed seven times, his symptoms improved. He was given cyclosporine and oral prednisolone as maintenance therapy. Two weeks later, his respiratory symptoms worsened. A chest HRCT revealed extensive subpleural GGO with bronchiolectasis and bronchiectasis, and a chest computed tomography angiography also found thrombi along the right internal and external jugular veins, superior vena cava, and right atrium, and pulmonary emboli were detected at the basal segment branches of both pulmonary arteries. Plasma exchange was restarted, and heparin was given but he did not respond to treatment. He died 44 days after diagnosis.

Case 5

A 49-year-old male, non-smoker with HT and DLP, presented with chronic cough and skin rash for two months and low-grade fever for one week. His physical examination showed a photosensitive rash. Lung auscultation revealed fine crepitation in the left lower lung. A CXR revealed GGO in the left lower lung and a chest HRCT showed GGO with some consolidation in lower lungs (Fig. 1E). His pulmonary function test (PFT) showed a moderate restrictive ventilatory defect and reductions in diffusion capacity. His anti-MDA5 antibody test was positive. He was diagnosed with CADM-ILD and treated with mycophenolic acid, azathioprine, cyclophosphamide, and prednisolone 10 mg/day. His symptoms and PFT improved and a follow-up HRCT showed stable multifocal subpleural GGO. He is still alive 12 months after diagnosis.

Case 6

A 58-year-old female, non-smoker with well-controlled asthma, presented with two months of chronic symmetrical polyarthralgia, skin rash, productive cough, progressive dyspnoea, and low-grade fever. Physical examination showed Gottron's sign and V-sign. Lung auscultation revealed fine crepitation in both lower lungs. A CXR revealed GGO in both lower lungs and a chest HRCT showed peripheral GGO, reticulations, and bronchiolectasis in both

lungs (Fig. 1F). Her anti-MDA5 antibody test was positive. She was diagnosed with CADM-ILD and treated with mycophenolic acid and prednisolone 30 mg/day. Her dyspnoea did not improve. Following rituximab, a follow-up chest HRCT showed decreased GGO and her symptoms improved. She is still alive 27 months after diagnosis.

Discussion

CADM can be found in about 20% of patients with DM. CADM with anti-MDA5 antibody was reported in 50–70% of patients with CADM [2,4]. Anti-MDA5 antibody is a type of myositis-specific autoantibody and reported to be a prognostic marker of RP-ILD in patients with CADM [4,5]. RP-ILD is associated with high mortality rates of up to 50%, especially within six months of diagnosis [2,3].

To our knowledge, limited data are available from case reports of patients with CADM-ILD. We report the first case series in Thailand of six patients diagnosed with CADM-ILD. All six patients in our series had CADM with anti-MDA5 antibody-positive ILD. Four patients had RP-ILD and three patients died due to progressive RP-ILD within seven weeks of admission. All of them had RP-ILD before the diagnosis of CADM.

The clinical features of our patients mostly presented with respiratory symptoms such as dyspnoea or cough at initial presentation, These findings were similar to other case reports [3,4,6,7]. However, some patients also had the cutaneous manifestations of CADM which were detected by physicians at first visit. Typical chest radiographic findings in this series were subpleural basal predominant GGO or consolidation, or both, which were similar to other case reports [1–3]. Pneumomediastinum was found in case 2 and was previously reported to be a poor prognostic marker of CADM-ILD [2].

Due to limited data on this disease, no treatment guidelines or consensus recommendations are available. From previous case reports, treatments used were combinations of immunosuppressive drugs including high-dose glucocorticoids, intravenous cyclophosphamide, and oral cyclosporine [3,4,6,7]. Rituximab and tofacitinib were also previously reported to have benefits in refractory anti-MDA5 antibody-positive ILD in patients with DM [8,9]. Plasma exchange can result in marked improvement in skin and respiratory symptoms in refractory anti-MDA5 antibody-positive ILD in patients with DM [10]. Treatments in our patients were combination therapies of immunosuppressive drugs. Two patients received rituximab and one patient underwent plasma exchange. None of our patients received Extracorporeal membrane oxygenation (ECMO) due to limited data from cost-effectiveness. However, the number of cases presented here is too small to make a conclusion for the treatment for this disease.

Ferritin was reported to be a useful biomarker to evaluate the response of treatment and the status of ILD in patients with anti-MDA5 antibody-positive ILD [11]. In this present series, two patients with RP-ILD had persistent rising serum ferritin, whereas two patients with RP-ILD and two with ILD had decreasing levels of ferritin after treatment.

In summary, patients with anti-MDA5 antibody-positive CADM usually present with respiratory symptoms with rapid deterioration or RP-ILD. As RP-ILD is associated with a high mortality rate, an early diagnosis is important to initiate treatment in these patients.

Disclosure Statements

Appropriate written informed consent was obtained for publication of this case series and accompanying images.
This study was approved by Office of Human Research Ethics Committee, Faculty of Medicine, Prince of Songkhla University (REC.63-224-14-1).

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