Anti-MDA5 Antibody-Positive Dermatomyositis

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ABSTRACT:

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Dermatomyositis is an autoimmune disease, in which positive anti-melanoma differentiation associated gene 5 (anti-MDA5) is known as serious subtype, that might develop mucocutaneous lesions, vascular occlusion, and rapidly progressive interstitial lung disease. We report case series of three middle-aged female dermatomyositis patients with positive anti-MDA5 serology. All of the patients had mucocutaneous lesions, composed of cutaneous ulcers together with Gottron's papules, and rapidly progressive interstitial lung disease. Histopathology of the ulcerated skin showed vascular thrombosis that was a common finding in this subtype. Patients were treated with several immunosuppressive drugs such as high-dose glucocorticoid, intravenous cyclophosphamide and azathioprine, however the disease progressed and two patients succumbed to their illnesses.

Key words: Anti-MDA5 dermatomyositis

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Dermatomyositis is an autoimmune disease that generally involves the cutaneous, proximal part of the muscle, myocarditis, higher risk of malignancy and occasionally the lung parenchyma[1]. Recently, anti-melanoma differentiation associated gene 5 (MDA5) was noted as a serious subtype of dermatomyositis that might develop as mucocutaneous, vascular occlusion, and rapidly progressive interstitial lung disease[2]. The prevalence ranged from 7-27% with over 50% mortality rate at 6 months[3]. The clinical characteristics and serious complications were different from the typical cutaneous dermatomyositis. An early detection of the disease may be helpful since prompt treatment might improve the patients' outcomes[2].

We report case series of three dermatomyositis patients with MDA5 serology positive.

Case 1

A 53-year-old Thai woman complained of pain at the distal interphalangeal joints of both hands for one year. She has been treated with oral diclofenac. One month prior to consultation, she developed erythematous papules and plaques on scalp, face, trunk, both elbows, knuckles (Figure 1). There were stellate-shaped necrotic plaques, 0.5-1 cm. in diameter, on the upper and lower back. She also had fever, arthralgia and 5-kg weight loss in 1 month. Two weeks later, she developed dyspnea on exertion but no muscle weakness. The physical examination of muscle revealed grade V of motor power in all extremities. She was then referred to Pharmongkutklao hospital and initially diagnosed as amyopathic dermatomyositis.

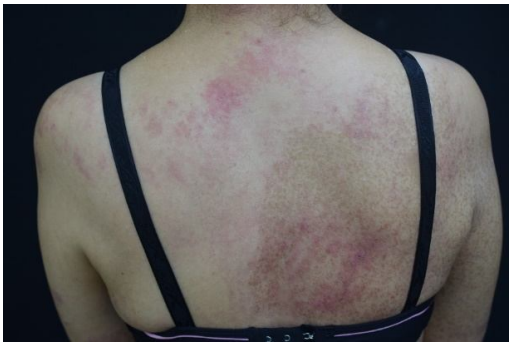

Figure 1 Multiple ill-defined erythematous papules and plaques at upper-mid back.

Laboratory investigation showed positive for anti-MDA5 (1+) and anti-Ro52. Anti-nuclear antibody showed positive coarse speckle 1:160. The serum CPK level was 169 U/L. electromyography (EMG) or muscle biopsy was not done.

The high-resolution computerized tomography (HRCT) of the chest showed diffuse ground-glass opacity, subpleural reticular opacity and traction bronchiectasis of both lungs, prominent at posterior aspect of both lower lobes. Histopathology from skin biopsy (back area) showed ulcer, focal interface vacuolar changes at the dermo-epidermal junction (DEJ) with

lymphocytes and hyalinized basement membrane. Direct immunofluorescence showed linear granular deposition at DEJ 1^+ - 2^+ of C_3 and fibrinogen. She was treated with hydroxychloroquine (HCQ) 200 mg/day

Two weeks later, she developed multiple ulcers on her back, extremities, and hard palate. She was treated with 1 mg/kg/day of prednisolone and 2 cycles of intravenous cyclophosphamide (IVCY) (800 mg/cycle). 3 weeks after treatment, the mucocutaneous lesions and respiratory symptoms were improved.

Case 2

A 59-year-old Thai woman with underlying rheumatoid arthritis which was diagnosed (in 2004/ 14 years earlier) and treated with oral 5 mg of methotrexate weekly. She developed progressive dyspnea on exertion, dry cough, and erythematous plaque at knuckles of both hands over 1-month duration (Figure 2,3,4). Later, her dyspnea got worse and there were erythematous plaques on her chest and upper back. Chest X-ray revealed reticular infiltration of both lower lungs. She was treated as pneumonia by her physician and referred to our hospital for further management.

Physical examination revealed fine crepitation of the lower lungs and erythematous plagues at knuckles, V-area. Motor power grade v all. Chest X-Ray showed thick reticular opacities, ground-glass opacities, peribronchial wall thickening together with traction bronchiectasis of both lungs with basal and peripheral predominance. Thus, she was diagnosed as overlap syndrome of rheumatoid arthritis and amyopathic dermatomyositis with interstitial lung disease. Her anti-MDA5 antibody was also positive (3+). The serum CPK level showed 38 U/L. EMG or muscle biopsy was not done.

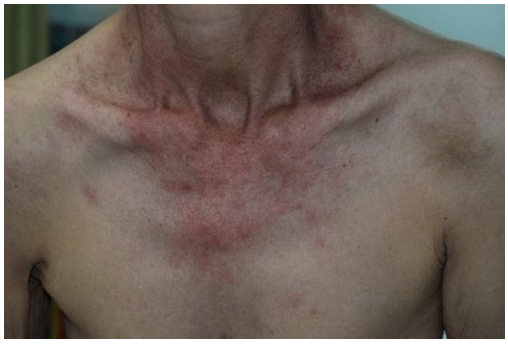

Figure 2 Multiple ill-defined erythematous patches and plaques at V-area. (V-sign)

She was initially treated with intravenous dexamethasone (8 mg/day) for 8 days, followed by prednisolone (1 mg/kg/day), then intravenous cyclophosphamide 500 mg/cycle for 6 cycles but the symptoms progressed. Six months after treatment, she developed tender subcutaneous nodule at the right leg. The skin biopsy showed lobular panniculitis with lymphocytic and neutrophilic infiltrations. Line probe assay for Non-Tuberculosis Mycobacterium from tissue

biopsy identified *Mycobacterium intracellulare* and *Mycobacterium scrofulaceum*. Hence, she was treated with clarithromycin (1 g./day), ethambutol (1 g./day) and rifampicin (600 mg./day).

3 months later, she had progressive dyspnea for 2 weeks and was initially empirical treated with intravenous antibiotics for pneumonia and dexamethasone (16 mg./day) for disease progression. Unfortunately, her symptom still was not improved and resulted in respiratory failure. Finally, she passed away due to septic shock.

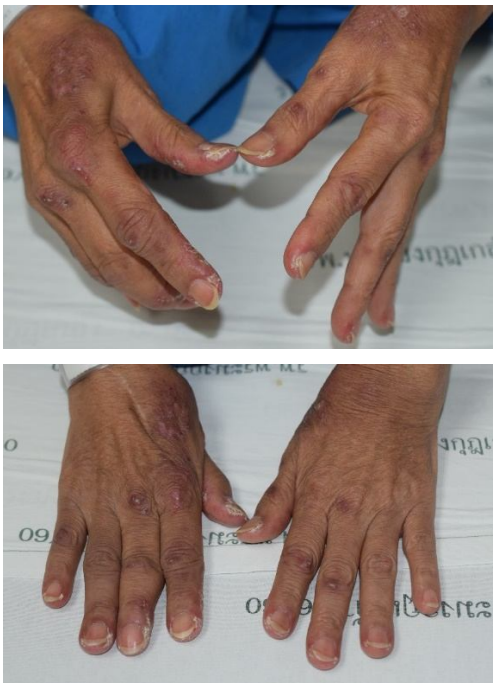

Figure 3,4 Multiple ill-defined erythematous plaques with scale at knuckle areas. (Gottron's papule)

Multiple ill-defined erythematous papules with keratotic scale at digital pulps and the radial aspect of the index finger. (Mechanic's hand)

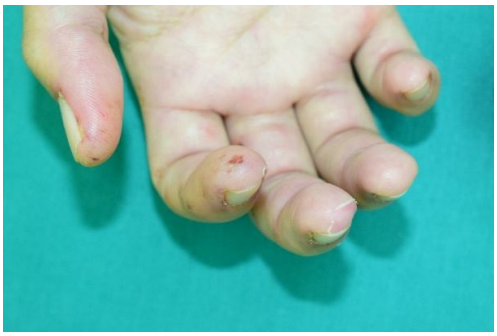

Figure 5 Ill-defined erythematous papule with central necrosis at tip of the index finger.

Case 3

A 42-year-old Thai woman presented with rashes and wounds at tips of the fingers for 3-weeks. The skin biopsy at the wound showed vascular thrombosis with fibrinoid deposit without vascular destruction and the skin biopsy from rash at elbow showed focal interface vacuolar change with atrophic epidermis, superficial perivascular infiltration with lymphocytes and mucin materials are present in the mid dermis (interface dermatitis). The only abnormal laboratory investigation was a low C3 level. She was diagnosis as connective tissue disease suspected systemic lupus erythematosus. As a consequence, we started prednisolone 20 mg/day and titrated up to 45 mg/day.

2 months later, she developed dyspnea. A physical examination revealed late inspiratory crackles bilaterally in both lower lungs, erythematous to purpuric papules with central atrophic ulcers at all distal fingers (Figure 5) and well-defined erythematous plaques with central necrotic crust on both elbows. Motor power at least grade IV all. Computerized tomography (CT) of the chest showed ground-glass opacity with regular interlobular septal thickening at the periphery and dependent parts of both lungs, more prominent on both lower lobes. Her anti-MDA5 serology was positive (2+). The serum CPK level revealed 25 U/L. EMG or muscle biopsy was not done. She was diagnosed with mixed connective tissue disease with amyopathic dermatomyositis and SLE.

Table 1

case	Sex	age	Disease duration	Cutaneous finding	Systemic finding	Specific antibody	treatment	Serum ferritin	Vital status
1	F	53	2 mo.	V-sign Gottron sign at knuckle, elbow Ulcer on back, extremity Oral ulcer	Interstitial lung disease	AntiMDA5 1+ Anti-Ro52 1+	HCQ 200mg/d Corticosteroid IVCY 2 cycle	-	alive
2	F	59	1 year	V-sign, shawl sign Gottron sign& papule at knuckle, elbow Holster sign Oral ulcer Ragged cuticle Mechanic hand Cutaneous ulcer at leg	Interstitial lung disease	AntiMDA5 3+ Anti-Ro52 1+	CQ 250mg/d Corticosteroid IVCY 6 cycle	500ng/mL	dead
3	F	42	5 mo.	Cutaneous ulcer on Gottron papule at elbow Erythematous papule at tip of fingers Malar rash Non-scarring alopecia	Interstitial lung disease	AntiMDA5 2+ Anti-Ro52 3+	Corticosteroid Azathioprine 50mg/d*1mo MMF 500-1000 mg/d*4d IVCY 1cycle Cyclosporine 100 mg/d*4d	-	dead

Summary of the patients

F = female HCQ = hydroxychloroquine CQ = chloroquine IVCY = intravenous cyclophosphamide

She was initially treated with antibiotics (ceftriaxone, azithromycin) for pneumonia and intravenous dexamethasone 8 mg/day for disease progression. After 16 days of treatment without improvement, pulse methylprednisolone 500 mg/day for 3 days and mycophenolate mofetil 1g/day in combination with dexamethasone 16 mg/day were given.

After 1-month of admission, her respiratory symptom continued to get worse. Finally, intravenous cyclophosphamide 500 mg and cyclosporine A 100 mg/day were given. Unfortunately, she did not respond to any treatment and passed away on the 50th day of admission to the hospital.

We reported cases of 3 amyopathic dermatomyositis patients with anti-MDA5 positive. All patients had common clinical presentation of rapidly progressive interstitial lung disease.

The clinical presentation and treatment summary of the patients are shown in the table1.

Discussion

Dermatomyositis (DM) is a systemic autoimmune disease which frequently affects cutaneous and neuromuscular systems. Skin manifestations compose of pathognomonic signs i.e. Gottron's papules and Gottron's sign, characteristic signs i.e. heliotrope, V-sign and shawl sign. The other cutaneous lesions that can be observed in DM patients i.e. periungual telangiectasias, mechanic's hands, poikiloderma, and calcinosis cutis. Systemic involvement such as internal malignancy affects approximately 25%[6]and interstitial lung disease (ILD) can occur in up to 50% of patients[7]. Amyopathic DM is a clinical term to describe patients who have cutaneous manifestations without muscle weakness or elevation in muscle enzymes for more than 6 months[8].

Anti-melanoma differentiation associated gene 5 (MDA5) positive DM is a unique subtype of clinical amyopathic DM, first described by Sato et al in 2005[9]. The prevalence is significant higher Asian population and is associated with a high frequency of ILD (90–95%), especially rapidly progressive ILD (RP-ILD) (50–80%)[10], that is accompanied by a more severe disease course, RP-ILD that is resistant to immunosuppressive therapy and more fatality[11].

The characteristic cutaneous ulceration in anti-MDA5 DM presentation on specific preexisting cutaneous lesions such as Gottron’s sign and Gottron’s papules involving the digital pulp, nail fold, elbows and knees. Less commonly, ulcer might occur on sun-exposed area such as upper chest, upper back and arm. The location of cutaneous ulcers at digital pulps and periungual areas are the most highly suggestive evidence for anti-MDA5-positive DM. Moreover, the ulceration is the strongest predictor of developing interstitial lung disease. The association between cutaneous

ulcers and increased risk of ILD in anti-MDA5-positive DM can be explained by the underlying systemic vasculopathy[11]in which the vascular occlusions are identified at the small and medium dermal vessels. Other clinical findings are non-scarring alopecia, panniculitis, mechanic's hand[12] arthritis, arthralgia, and fever[10]. RP-ILD is a mortal systemic complication that shows poor prognosis due to respiratory failure[10].

ILD with rapid progression is a mortal systemic complication[10]. Although the precise pathogenesis remains unclear but that might be associated with the result of the vasculopathy and anti-MDA5 antibodies[12] and endothelial cells are target of anti-MDA5 antibodies which is hypothesized that endothelial cell damage leads to produce various mediators of fibrosis-one report of patients with DM and polymyositis showed that levels of transforming growth factor-β (a profibrotic cytokine) strongly correlate with other markers of endothelial cell damage and give a mechanistic link between endothelial cell damage and fibrosis[13]. Furthermore, anti-Ro52 antibodies has recently been reported in anti-MDA5-positive ILD patients[14]. The relation of anti-Ro52 is a costimulatory autoantibody, a concept reported in patients with anti-synthetase syndrome[15,16]. The preferred investigation is HRCT chest and lower consolidation/ground glass appearance pattern are associated with short term mortality[17]. According to our patients, they present with progressive dyspnea in early 3 months of onset with chest CT or HRCT chest revealed ground glass opacity.

Predicted poor prognosis is ferritin. The strength of this association increased with elevated ferritin level (≥1600 ng/mL)[18]. The investigation was performed in only one patient (No.2) at ferritin 500 ng/ml. Moreover, high level of IL-18 could be referred to the poor prognosis. Thus, serum ferritin level and IL-18 level are useful for evaluating the response to treatment[19]. Moreover, high levels of anti-MDA5 antibodies at diagnosis are useful for predicting poor outcomes and the reduction and subsequent disappearance of antibodies during the course of immunosuppressive treatment are associated with favorable outcomes. The present study shows the correlation between high antibody levels and RP-ILD. Hence, the anti-MDA5 antibody ELISA will be useful for early diagnosis, timely prediction of RP-ILD development, monitoring disease activity and evaluating therapeutic efficacy[20].

Recently, the treatment guideline of anti-MDA5 DM has not been established yet. The treatments depend on the degree of disease severity. A combination of immunomodulators and immunosuppressants is needed[4]. The administration of intensive immunosuppressive therapy prior to irreversible pulmonary damage might improve the prognosis of RP-ILD in patients

with DM. Early induction of combined immunosuppressive therapy consisting of high dose corticosteroids, intravenous cyclophosphamide and calcineurin inhibitors may improve survival[21]. The other immunosuppressive drugs, including mycophenolate mofetil. Other treatments such as, rituximab, intravenous immunoglobulin[4] and short-term plasma exchange[22] may be effective for this disease but the efficacy of these treatments has not yet been fully established. In patients with severe or recalcitrant pulmonary disease may be treated with rituximab, cyclophosphamide, or other agents. Vasodilator (nifedipine, sildenafil) and improved peripheral circulation drugs (e.g., aspirin and pentoxifylline) may be helpful for treating this disease[4].

In conclusion, we report the case series of three Thai women in Phramongkutklao Hospital. All of patients have anti-MDA5 positive and rapidly progressive interstitial lung disease. They were received several treatments so early intervention and aggressive treatment are need.

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