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Case report

Erythematous auricular papules in the fatal cases of anti-MDA5 antibody-positive interstitial lung disease

Porntip Intapiboon, Boonjing Siripaitoon *

Allergy and Rheumatology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, HatYai, Thailand

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ABSTRACT

Introduction/objectives: The anti-melanoma differentiation-associated gene 5 (Anti-MDA5) antibody is associated with rapidly progressive interstitial lung disease (RP-ILD) and clinically amyopathic dermatomyositis (CADM). The predictors of treatment response would help in classifying the subgroups and decision-making. Here, we aimed to report an observational skin lesion that might be associated with a grave prognosis in six patients with anti-MDA5 antibody-positive ILD.

Methods: This case series included 6 anti-MDA5 antibody-positive ILD patients, who were admitted to Songklanagarind Hospital between January 2018 and June 2020. Their medical records were reviewed for clinical phenotypes, laboratory results, imaging studies, treatment, and outcomes. The cutaneous manifestations associated with fatal outcomes were observed and reported.

Results: Among 6 patients with anti-MDA5 antibody-positive ILD, 5 patients had CADM and one patient had no skin involvement. Four patients manifested as RP-ILD within a few months. Three deaths occurred despite highly intensive immunosuppressive treatment. All the patients in the dead group exhibited erythematous papules on their auricles and a presence of pulmonary consolidation at lower lung fields was additionally observed.

Conclusion: Erythematous auricular papules may be a hallmark of grave prognosis in anti-MDA5 positive CADM with ILD.

1. Introduction

The anti-melanoma differentiation-associated gene 5 (anti-MDA5), formerly known as an autoantibody against the 140-kDa protein, has been identified in a subgroup of patients with clinically amyopathic dermatomyositis (CADM) [1]. It is useful to predict the prognosis of patients with CADM-complicated rapidly progressive interstitial lung disease (RP-ILD) [2]. This condition exhibits a dermatomyositis (DM) rash including cutaneous ulcerations and/or palmar papules [3] and interstitial lung disease (ILD) either in the chronic form or RP-ILD [4]. The dermato-pulmonary syndrome associated with anti-MDA5 antibody appears to exhibit high hospital mortality [4,5]. It has been observed that nearly half of the individuals with anti-MDA5 antibody-associated ILD died within a short period of respiratory symptom onset [6]. Moreover, the appropriate treatment strategy is still a matter of debate.

In this report, we present six patients with anti-MDA5 antibody-associated ILD. A total of three patients were diagnosed with CADM complicated by RP-ILD and finally died within three months despite intensive immunosuppressive agents. We now report on an observational cutaneous sign that might be associated with poor prognoses in these patients.

2. Methods

2.1. Patients

This case series included six adult patients with anti-MDA5 antibody-positive ILD, who were admitted to Songklanagarind Hospital, Prince of Songkla University, Thailand, between January 2018 and June 2020. All the patients were diagnosed, provided with treatments, and followed up by the rheumatologists (BS, PI). This study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (study code 3033/63-342-14-1). Written informed consent was obtained from the patients or relatives for the publication of this case series, including their photographs.

* Corresponding author. Allergy and Rheumatology Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, 15 Kanjanavanich Road, HatYai, Songkhla, 90110, Thailand.

E-mail addresses: iporntip@medicine.psu.ac.th (P. Intapiboon), sboonjin@medicine.psu.ac.th (B. Siripaitoon).

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2.2. Variables and definitions

CADM was diagnosed if there were typical DM skin lesions, with no clinical evidence of muscle disease, and/or subclinical evidence of myositis [7]. ILD was diagnosed based on the results of chest radiography and chest computed tomography (CT). RP-ILD was defined upon the presence of progressive dyspnoea and hypoxaemia, and a worsening of interstitial changes on the chest radiograph within 1 month from the onset of respiratory symptoms [1].

The data included the sex, age, clinical symptoms, physical signs, and initial laboratories, including muscle enzymes and ferritin levels. The autoantibodies comprised antinuclear antibodies (ANA) using an immunofluorescence method and myositis antibodies using a commercial immunoblot assay (EUROLINE autoimmune inflammatory myopathies 16 Ag, EUROIMMUN, Lübeck, Germany). Chest radiography and high-resolution computed tomography (HRCT) interpretation were performed by an experienced radiologist.

2.3. Treatment and outcomes

Treatment strategies depended on the severity of the disease and decision of the physicians. All patients received corticosteroids with or without 1–3 days of methylprednisolone (IVMP) and immunosuppressive drugs, including cyclophosphamide, cyclosporin A (CSA), and mycophenolate mofetil (MMF). The outcomes were classified as alive or dead. Poor and favourable prognostic markers were also identified.

3. Results

The clinical features of six patients with anti-MDA5 antibody-positive ILD are summarised in Table 1. CADM was observed to manifest in five of the patients. The median age was 52.5 years (range, 36–63 years), and the proportion of women to men was equal. Five patients presented with a prolonged febrile illness, polyarthritis, and a typical DM rash, including heliotrope rash, Gottron's sign or papules, periungual erythema, photosensitivity rash, and mechanic's hands. Skin ulcers over the Gottron's sign were observed at the knuckles (Fig. 1E) and elbows in one case (Case 3). Notably, we observed erythematous papules at the helix and/or antihelix of the auricles in three patients (Cases 1–3) (Fig. 1A and 1C). This auricular lesion led to a misdiagnosis of systemic lupus erythematosus (SLE) prior to CADM diagnosis (Case 3).

3.1. Pulmonary manifestations

Among all the patients manifesting pulmonary symptoms, four patients were finally diagnosed with RP-ILD, and two patients with classic ILD. All the patients presented with clinically progressive dyspnoea and dry cough. Oxygen desaturation was observed in all patients with RP-ILD. In the RP-ILD subgroup, HRCT of the chest revealed organising pneumonia, ground-glass opacity (GGO), as well as the presence of consolidations predominately located in the lower lungs (Cases 1–4) (Fig. 1B, 1D and 1F). In addition, complicating pneumothorax and pneumomediastinum were observed in one case (Case 3). In contrast, there was a non-specific interstitial pneumonia (NSIP) pattern on HRCT in the ILD subgroup.

3.2. Laboratories and serology data

It was observed that four of the five CADM patients displayed an

Table 1
Clinical manifestations, imaging, laboratories, treatment administered, and outcomes.

Characters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age/Gender	63/M	46/M	36/F	59/F	62/F	49/M
Diagnosis	CADM, RP-ILD	CADM, RP-ILD	CADM, RP-ILD	RP-ILD	CADM, NSIP	CADM, NSIP
Weakness	No	No	No	No	No	No
Fever	Yes	Yes	Yes	No	Yes	Yes
Arthritis	Yes	Yes	Yes	Yes	Yes	Yes
Heliotrope rash	Yes	Yes	Yes	No	No	No
Gottron's sign/papules	Yes	No	Yes	No	Yes	Yes
Photosensitivity rash	Yes	Yes	Yes	No	Yes	Yes
Periungual erythema	Yes	Yes	Yes	No	Yes	Yes
Mechanic's hand	Yes	Yes	No	No	Yes	Yes
Skin ulceration	No	No	Yes	No	No	No
auricular papules[a]	Yes	Yes	Yes	No	No	No
RP-ILD	Yes	Yes	Yes	Yes	No	No
HRCT pattern	OP	OP	OP	OP	NSIP	NSIP
Consolidation on HRCT	Yes	Yes	Yes	Yes	Yes	No
GGO on HRCT	Yes	Yes	Yes	Yes	Yes	Yes
ANA (titer)	negative	1:80	1:640	negative	1:80	negative
Anti-Ro52	positive	positive	positive	positive	negative	negative
CK, IU/L (0–190)	187	404	282	482	97	100
Ferritin, ng/ml (30–400)	1372	6872	1102	2129	335	1944
LDH, U/L (240–480)	834	689	1023	922	565	–
Aldolase, U/L (4–12)	5.5	17.9	17.9	12.2	15.5	–
Treatment	IVMP, PSL IVCY, CSA, TPE	IVMP	IVMP, PSL, CSA, MMF, Rituximab	IVMP, PSL, CSA, IVCY, MMF	PSL, CYC	PSL, MMF Rituximab
Survival time (wks)	6	1	11	66	70	44
Outcome	dead	dead	dead	survived	survived	survived

ANA; antinuclear antibody, OP; organising pneumonia, CADM; clinically amyopathic dermatomyositis, CK; creatinine phosphokinase, CSA; cyclosporine A, CYC; cyphophosphamide GGO; ground glass opacity, HRCT; high-resolution computed tomography, IVCY; intravenous cyclophosphamide, IVMP; intravenous pulse methylprednisolone, LDH; lactate dehydrogenase, MMF; mycophenolate mofetil, NSIP; nonspecific interstitial pneumonia, PSL; prednisolone, RP-ILD; rapidly progressive interstitial lung disease, TPE; therapeutic plasma exchange, wks;weeks.

[a] Erythematous auricular papules at helix/antihelix.

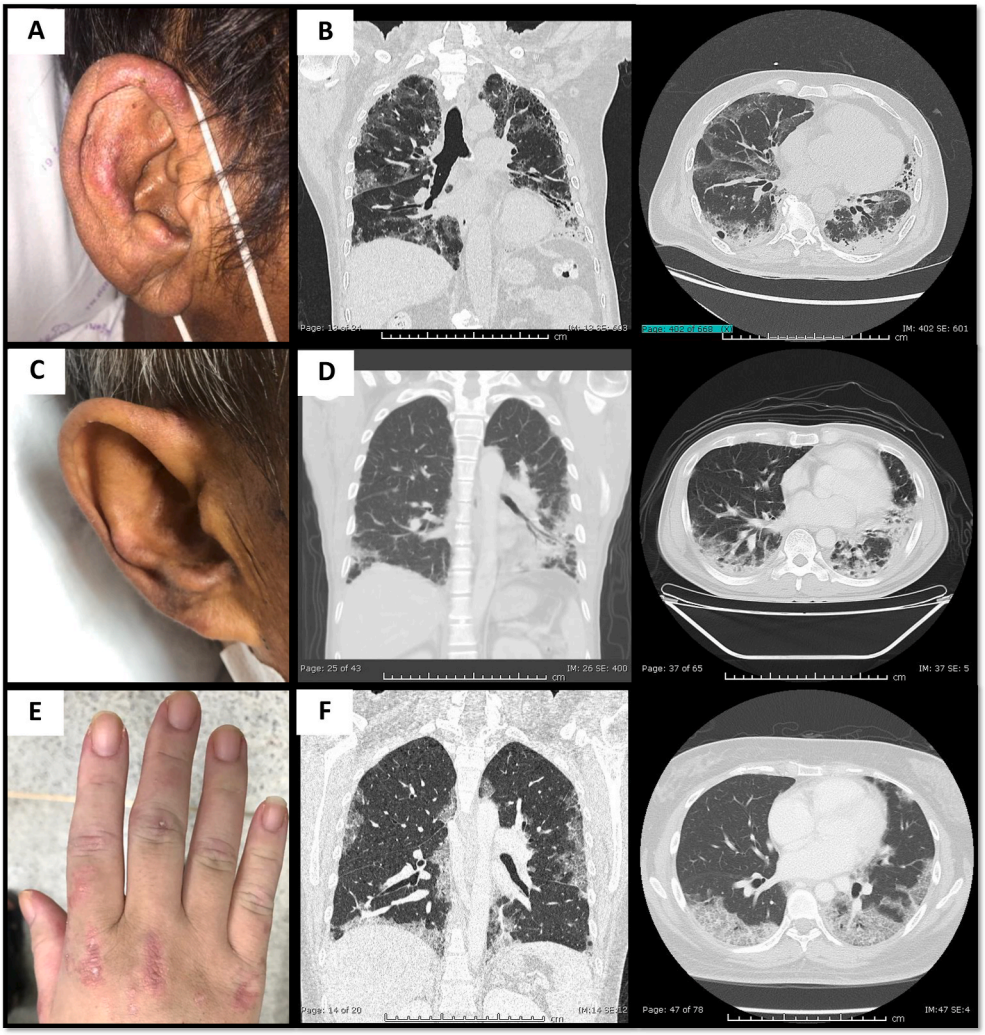

Fig. 1. Images of patients with fatal RP-ILD in anti-MDA5 antibody-positive lung disease (A) erythematous auricular papules at helix and antihelix, and necrotic ulcer at antitragus area of right ear, and (B) chest HRCT finding of diffuse subpleural ground-glass opacity and predominately lower lung consolidation and reticulation (case 1), (C) erythematous rash at helix and antihelix of right ear, and (D) chest HRCT finding of bibasilar consolidation and reticulation (case 2), (E) skin ulceration overlying on the Gottron's sign over the right third knuckle, and (F) chest HRCT finding of subpleural ground-glass opacity and consolidation, with accompanied by pulmonary hypertension (case 3).

mildly elevation of creatinine phosphokinase (CK) (median 234.5 IU/L [range, 97–482 IU/L]) and aldolase (median 15.5 U/L [range 5.5–17.9 U/L]), which were compatible with hypomyopathic DM [7]. The ferritin levels were observed to be elevated in all six patients (median, 1658 ng/dL [range 335–6872 ng/dL]) as well as lactate dehydrogenase level (LDH) (median 834 U/L [range 565–1023 U/L]). Only one (16%) patient exhibited positive ANA; however, up to four (66%) patients showed positive anti-Ro52 antibody results.

3.3. Treatment data

All patients received a high dose of corticosteroids combined with immunosuppressive drugs for ILD. Among RP-ILD patients, three cases were prescribed IVMP; two of them were treated with a combination of intravenous cyclophosphamide (IVCY) and CSA 4 mg/kg/day (Cases 1 and 4), and one patient received rituximab combined with CSA 4 mg/kg/day and MMF 2 gm/day (Case 3). The last patient in the RP-ILD group received only a single dose of IVMP before his early death (Case 2). In the NSIP-ILD subgroup, the regimens consisted of a medium-dose of corticosteroids combined with oral cyclophosphamide (Case 5) and rituximab with MMF 2 g/day (Case 6) (Supplementary Table S1).

Three (75%) RP-ILD patients died within three months of diagnosis (Cases 1–3); two patients died due to disease-related causes and one patient died due to septicaemia. Overall, three patients survived with improved respiratory function, ability to perform daily activities, and there was no need for long-term oxygen therapy. The median survival time was 27.5 weeks (min-max: 1–70 weeks).

In our case series, we observed that erythematous auricular papules at either the helix or antihelix were hallmark skin manifestations associated with fatal outcomes in anti-MDA5 antibody-positive CADM with ILD.

4. Discussion

RP-ILD is an under-recognised but critical complication in the anti-MDA5 antibody-associated disease, which is characterised by a variable clinical spectrum and difficulty in predicting the response to therapy. Our case series reported three cases with rapidly fatal outcomes and the other three cases had better outcomes. We highlighted an observational finding that all the fatal cases in our study had erythematous auricular papules prior to developing RP-ILD. Additionally, HRCT of the chest showed lower lung consolidation, which is more common in the fatal group.

Auricular skin lesions in the anti-MDA5-associated disease have seldom been mentioned in literature. Until recently, antihelix/helix violaceous macules were reported in 6 of 9 patients with anti-MDA5, whereas they were not found in the 41 patients with other myositis-specific antibodies [8]. These six patients had ILD, and one patient died from RP-ILD despite intensive treatment. In another report, the prevalence of antihelix/helix lesions in DM patients with anti-MDA5 was higher than that in DM patients without anti-MDA5 (40.7% vs 18.6%; $p < 0.05$) [9]. All patients in the anti-MDA5 group had ILD, and 57%

suffered from RP-ILD. Palawisuth et al. published a case of anti-MDA5 positive DM with fatal RP-ILD who also had erythematous papules with ulcer on antihelices [10]. Herein, we concur with the previous reports that this auricular sign is a bad sign in DM patient and might predict a serious lung disease. Antihelix/helix, the protrusions of the auricles, are common sites for sun exposure and decubitus. Antihelix/helix papules would be triggered by microvascular injury induced by pressure, as are palmar papules (inverse Gottron's papules) around the interphalangeal joints [8]. Three key learning points from this report are: 1) this auricular skin sign may be misdiagnosed as a discoid rash in lupus; 2) this skin sign may also lead to a suspicion of anti-MDA5 antibody-related dermato-pulmonary syndrome, which may require early and prompt therapy, and 3) it may be associated with the recalcitrant form of lung disease.

Cutaneous ulcers and palmar papules are well recognised as distinctive cutaneous findings in anti-MDA5 antibody-associated CADM [3]. These lesions occurred in up to 30–80% of patients [3,6], which was reported more commonly in the Asian race [11]. The ulcer commonly occurs on the elbows, knees, lateral nail folds, or even overlying on the Gottron's papules [12], which may be extensive or complicating as ischaemic necrosis [3]. The mechanism behind this lesion was postulated as a result of underlying vasculopathy or microvascular injury, which has been systemically related to pneumomediastinum and poor survival [11]. Additionally, we found skin ulceration in one patient with accompanied fatal ILD and pneumomediastinum.

The RP-ILD ranged from 22% to 100% of anti-MDA5-associated lung disease in previous reports [12]. The common HRCT findings are GGO or consolidation predominated at subpleural, lower, or random distributions [13]. Organising pneumonia has also been reported up to three quarters [14]. In anti-MDA5-positive patients, the 90-day mortality was significantly higher in patients with lower lung consolidation/GGO pattern than in those without this pattern [15]. Likewise, we found organising pneumonia with lower lung consolidation in the dead group. Therefore, this finding could guide the intensive therapeutic modality.

Serum ferritin is commonly used as a biomarker to predict poor outcomes [16]. The speculated mechanism is the dysregulation of the MDA5 signalling pathway in innate immunity, leading to the development of macrophage activation and cytokine storm syndrome, which presented as fever, a pronounced inflammatory response, and lung damage. The observation of the ferritin levels is a practical and inexpensive tool for disease monitoring.

Anti-Ro52 was found in 75% of anti-MDA5 positive RP-ILD patients, higher than without RP-ILD (16%) [17,18]. Additionally, Temmoku et al. demonstrated higher mortality upon the combined presence of anti-SSA/Ro52 and anti-MDA5 [19], consistent with our series, all fatal cases exhibited anti-Ro52 positivity. Further studies should be conducted to clarify how anti-Ro52 is significantly associated with poor prognoses in CTD-related ILD.

Combination regimens including high-dose glucocorticoids and calcineurin antagonists with or without cyclophosphamide are recommended as a first-line therapy for anti-MDA5 antibody RP-ILD. Plasmapheresis, polymyxin B hemoperfusion, or intravenous immunoglobulins were considered rescue therapies for refractory cases [20]. However, despite intensive strategy, the mortality rate is still high. Thus, the appropriate regimen is still under debate. To the best of our knowledge, the strategies to improve survival should be: 1) an early recognition of the disease phenotype based on clinical clues, imaging, and biomarkers; 2) early intensive combination treatment; and 3) surveillance and management of infectious complications and macrophage activating syndrome. Further studies are essential to understand the disease pathogenesis that may be helpful in the design of new treatment modalities.

In summary, we presented a particular cutaneous phenotype, erythematous auricular papules that may be linked to fatal outcomes in anti-MDA5 antibody-positive lung disease.

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Ethics approval

The study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (study code 3033/63-342-14-1).

Consent for publication

The informed consent was obtained from the patients or relatives in cases for the publication of their photographs.

Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Porntip Intapiboon. The first draft of the manuscript was written by Porntip Intapiboon and Boonjing Siripaitoon commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101299.

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