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CASE BASED REVIEW

# Utilize lung ultrasound B-lines and KL-6 to monitor anti-MDA-5 antibody-positive clinically amyopathic dermatomyositis-associated interstitial lung disease: a case report and literature review

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## Abstract

In the past decade, lung ultrasound (LUS) B-lines and serum Krebs von den Lungen-6 (KL-6) antigen have been recognized as biomarkers of the connective tissue disease-associated interstitial lung diseases (CTD-ILDs). Robust data have demonstrated that B-lines total numbers and KL-6 levels are correlated with high-resolution computed tomography findings, pulmonary function test, and some clinical parameters in CTD-ILDs. However, limited data are available regarding the use of these two biomarkers to follow CTD-ILDs. Herein, we report a case with anti-melanoma differentiation-associated gene 5 antibody-positive clinically amyopathic dermatomyositis-associated ILD, successfully treated with high-dose methylprednisolone, cyclophosphamide, intravenous immunoglobulin, pirfenidone, and followed using lung ultrasound and KL-6.

**Keywords** Anti-MDA-5 antibody · B-lines · Clinically amyopathic dermatomyositis · Follow-up · Interstitial lung disease · KL-6

## Introduction

The diagnosis and management of anti-melanoma differentiation-associated gene 5 (MDA-5) antibody-positive clinically amyopathic dermatomyositis (CADM)-associated interstitial lung diseases (ILDs) remains a challenge in the rheumatic community because it is intractable, rapidly progressive, and has a poor prognosis [1, 2]. High-resolution CT (HRCT) is still an imaging "gold standard" to diagnose and follow the ILDs. However, the high radiation dose, cost and the large, non-portable equipment limit HRCT's clinical application to closely monitor the lung in this entity [3]. Recent data have demonstrated that lung ultrasound (LUS) B-lines and serum Krebs von den Lungen-6 (KL-6) antigen levels are correlated with HRCT findings, pulmonary function test (PFT), and some clinical variables in connective tissue disease-associated interstitial lung diseases (CTD-ILDs). Additionally, these two radiation-free and non-invasive biomarkers appear to have good sensitivity to detect early pulmonary changes in CTD-ILDs [4]. However, limited data are available regarding the use of these two biomarkers to follow CTD-ILDs.

Herein, we report a case with anti-MDA-5 antibody-positive CADM-associated ILD, successfully treated with high-dose methylprednisolone, cyclophosphamide, intravenous immunoglobulin, pirfenidone, and followed using lung ultrasound and KL-6.

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## Case report

A 42-year-old non-smoking woman was referred to our hospital after 1 month of rash, joint pain and swelling, dry cough, and progressive dyspnea on exertion. Treatment with Chinese traditional medicine and non-steroidal anti-inflammatory drugs (NSAIDs) ameliorated her symptoms temporarily. Two weeks before admission, non-productive cough and progressive dyspnea on exertion developed. She was given the azithromycin, ambroxol, and methoxyphenamine therapy, but symptoms worsened. On admission, her temperature was 37.2 °C, blood pressure 130/80 mmHg, pulse 102 beats per minute, respiration 28 per minute, and oxygen saturation was 93% in room air. Physical examination revealed periorbital heliotrope rash and erythematous rash over the metacarpophalangeal (MCP) and proximal inter-phalangeal (PIP) joints (Gottron's papules) (Fig. 1). Wrist, MCP, and PIP joints were symmetrically swollen and tender. There was no muscle weakness or muscle tenderness. Auscultation revealed Velcro rales in the lower lobes of the lungs. Initial PFT showed a restrictive pattern with a reduced diffusion capacity (forced expiratory volume in the 1st second [FEV1] 52.8%, forced vital capacity [FVC] 50.9%, total lung capacity 57.1%, diffusing capacity for carbon monoxide [DLCO] 20.2%). Arterial blood gas showed hypoxemia (PaO2 70 mmHg; PaCO2 32.5 mmHg; pH 7.42; SatO2 95.3%). On chest HRCT, bilateral ground-glass opacity and inhomogeneous infiltrates predominantly in the subpleural and basal regions were present superimposed on a background pattern consistent with non-specific interstitial pneumonia (NSIP) (Fig. 2). LUS examination including 50 scanning points revealed multiple B-lines (B-lines total number was 286), predominantly distributed in areas consistent with the HRCT (Fig. 2). Electromyography examination was normal. Laboratory findings showed a slightly elevated erythrocyte sedimentation rate (30 mm/H, reference < 15 mm/H) and C-reactive protein (13 mg/L, reference < 8 mg/L), hyperimmunoglobulinemia (IgG was 26 g/L, γ-globulin was 37.2%, reference < 15 g/and 20% respectively). Blood cell count, urine routine, complement, creatine kinase, ferritin, procalcitonin, culture of the sputum, T-SPOT, and tumor marker (including CEA, AFP, CA19-9, CA15-3, CA-125, and NSE) were normal. Screening for respiratory viruses was negative. Antinuclear auto-antibody (1:1000, cytoplasmic speckled pattern), anti-SSA, and anti-Jo-1 antibody were positive. Despite an initial dose of intravenous 40 mg methylprednisolone was given and Ceftriaxone 2.0 g was started empirically to cover potential infection, the patient's condition continued to worsen. Extended testing for myositis-specific and myositis-associated antibodies and biomarker for ILDs showed highly positive anti-MDA5-antibody and remarkably elevated serum KL-6 level (4089 U/ml, reference 105–435 U/ml). Ultimately, the diagnosis of anti-MDA5-antibody-positive CADM-associated ILD was established. High pulse dose methylprednisolone (500 mg IV for 3 days) was started, followed by a maintenance dose of 80 mg (IV daily for 1 week), and tapered to a dose of 40 mg po immediately thereafter. Immunosuppressive therapy with intravenous cyclophosphamide monthly (500 mg/m$^2$ body surface area), high-dose immunoglobulin (400 mg/kg for 5 days), and pirfenidone (300 mg, three times per day) were added and the patient's clinical condition including joint pain, rash, and dyspnea on exertion gradually improved. LUS obtained after 2 weeks of aggressive treatment showed total B-lines number was reduced to 220. Serum KL-6 value was decreased to 3050 U/ml. No follow-up HRCT of the lungs was done during hospitalization. After discharge, she continued to receive prednisone (40 mg daily and taper by reduction of 5 mg every 2 weeks), pirfenidone (300 mg, three times per day), and monthly intravenous cyclophosphamide (500 mg/m$^2$ body surface area). Six months later, chest HRCT showed complete resolution of ground-glass opacity and infiltrate lesion (Fig. 2). LUS follow-up B-lines had decreased to 59 (Fig. 2). Serum level of KL-6 was 911 U/ml. IV cyclophosphamide was stopped and cyclosporine A (100 mg twice daily) were begun while prednisone 10 mg/day was continued. She was also given proton-pump inhibitor lansoprazole, calcium, and vitamin D therapy. She remains asymptomatic and was followed up regularly for more than 1 year.

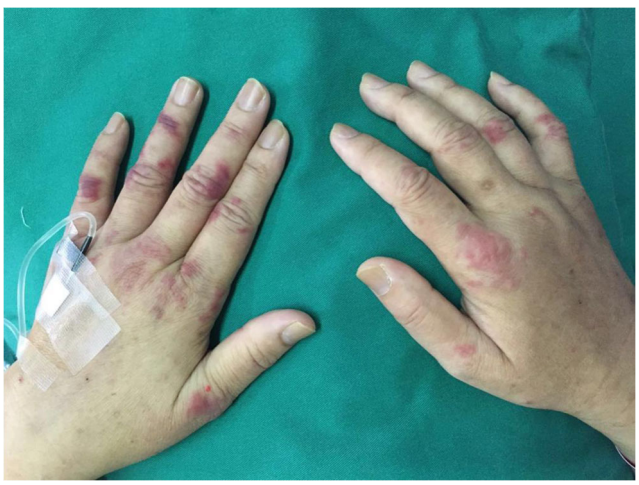

**Fig. 1** Gottron's papules

## Discussion

Anti-MDA-5 antibody-positive CAMD is a recently described myositis phenotype associated with rapidly progressive and refractory ILD plus rapid respiratory deterioration and extremely poor prognosis [5]. Although the pathogenesis and cause for the acute lung injury associated with this myositis subtype is not fully understood, early identification and

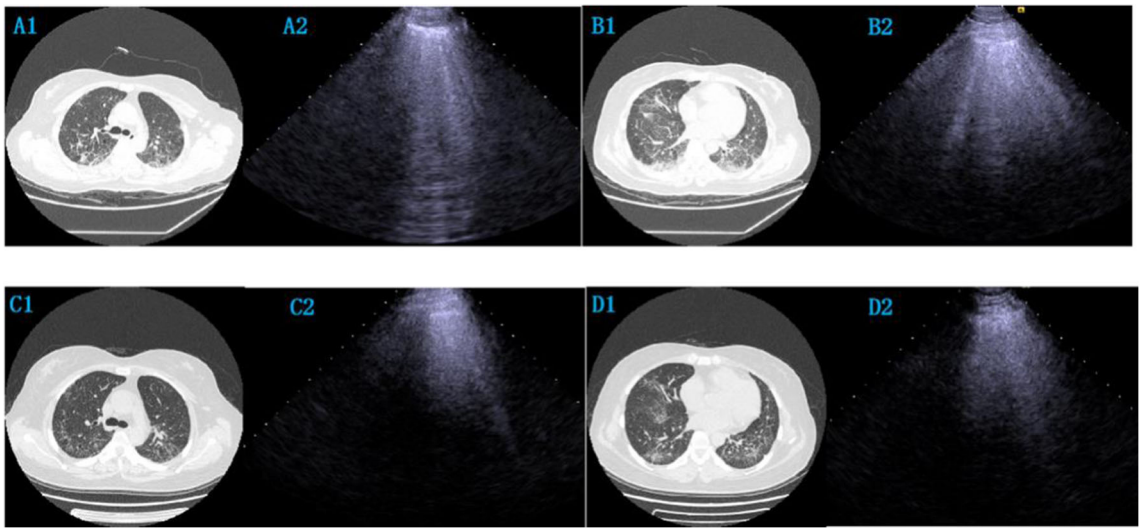


**Fig. 2** Chest HRCT and LUS before (A and B) and after (C and D) aggressive treatment. HRCT (A1 and B1) showing bilateral ground-glass opacity (GGO) and infiltrates predominantly in the subpleural and basal regions superimposed on a background pattern consistent with non-specific interstitial pneumonia. LUS at the third (A2) and fifth (B2) right posterior intercostal space showing multiple B-lines. Follow-up HRCT and LUS showing resolution GGO, infiltrated lesion, and B-lines

aggressive therapy may improve the prognosis [6, 7]. In addition, closely monitoring pulmonary changes should help improve treatment decisions.

To the best of our knowledge, this is the first case utilizing all of LUS, KL-6, and HRCT in the diagnosis and follow-up of anti-MDA-5-positive CADM-associated ILD. The case demonstrated that the changes in B-lines numbers and serum levels of KL-6 were consistent with the changes in HRCT findings and clinical presentation.

Previously two cases, systemic sclerosis (SSc)-associated ILD and rheumatoid arthritis (RA)-associated ILD also indicated that LUS is useful and radiation-free, and is a sensitive imaging modality to monitor CTD-ILDs [8, 9].

In the past decade, LUS has been extensively applied to screen and diagnose CTD-ILDs (majority of studies focused on SSc and RA) and is partially validated. Robust data showed LUS B-lines correlated well with HRCT Warrick score (partial criterion validity), PFT, and some clinical parameters (construct validity) [3]. LUS also has high sensitivity to identify early CTD-ILD change [10, 11]. Content validity, reliability, feasibility, and discrimination remain to be shown although content validity and feasibility should not be barriers [12]. Our data represent a first step toward validating responsiveness. Despite this lack of full validation, our data show the potential usefulness of lung ultrasound in this circumstance.

Data regarding LUS to monitor pneumonia and pulmonary congestion, particularly in children and emergency patients, are promising and encouraging [13–16]. However, no data are available associated with follow-up of CTD-ILDs. Nevertheless, Cappelli et al. have proposed a diagnostic algorithm including LUS for SSc-ILD screening [17]. SSc patient should undergo PFTs, HRCT at baseline and perhaps LUS should be added to this assessment, once it has been fully validated. Once validated, we feel that LUS should be considered for monitoring in the same way as PFTs as it is safer and less expensive than HRCT of the lungs. In those circumstances and with a validated measure, patients without lung involvement could then be monitored every 1–2 years (depending on the presence of risk factors) using PFTs and LUS. Patients with evidence of ILD could perform PFTs and LUS every 6 months; HRCT should be performed if progression of lung disease is suspected [17]. However, clinical presentations of CTD-ILDs are remarkably heterogeneous, so the interval of PFT and potential LUS follow-up may need to be flexible in the case of rapidly progressive ILD.

KL-6 is a mucin-like, high-molecular weight glycoprotein expressed on the surface membranes of type 2 alveolar epithelial cells and bronchial epithelial cells and increases following cellular injury and/or regeneration [18]. Previous studies revealed KL-6 could be a useful monitoring biomarker of CTD-ILDs activity and a significant predictor of deterioration of ILD [19–21]. In a recent study by Yamakaw H et al., 40 patients with SSc/mixed connective tissue disease (MCTD)-associated ILD were involved. Serum KL-6 concentrations correlated positively with DLCO and disease extent on HRCT, and the changes in serum levels of KL-6 were significantly related to the change in FVC. These findings indicated serum KL-6 could be a promising monitoring tool for SSc/MCTD-associated ILD activity [22]. Bandoh S et al. reported serum KL-6 concentrations were significantly higher in patients with ILD-associated with polymyositis (PM)/dermatomyositis (DM) compared with those without ILD. KL-6 levels were also found significantly increased in diffuse alveolar damage pattern than the NSIP pattern. KL-6 values in sera changed according to the progression or improvement of PM/DM-associated ILD [23].

Further in our recent study, B-lines were found positively correlated with serum KL-6 levels ($r = 0.54$, $p < 0.0001$) among 60 patients with CTD-ILDs. Additionally, both B-lines and serum KL-6 levels were significantly correlated with HRCT Warrick score ($r = 0.76$, $p < 0.0001$, and $r = 0.4$, $p < 0.0001$ respectively) and PFT variables ($r = -0.58$, $p < 0.0001$, and $r = -0.46$, $p < 0.01$ respectively for FEV1; $r = -0.59$, $p < 0.0001$, and $r = -0.42$, $p < 0.01$ respectively for FEV; $r = -0.67$, $p < 0.0001$, and $r = -0.49$, $p < 0.001$ respectively for DLCO). This finding suggests that the combined use of radiation-free imaging biomarkers and non-invasive serum biomarkers could be very useful modality to assess CTD-ILDs [4].

## Conclusion

In a patient with anti-MDA-5-positive CADM-associated ILD, combined use of HRCT, LUS, and KL-6 were used to follow aggressive therapy. These results indicate that the combined use of lung ultrasound and serum biomarkers like KL-6 might be a safe, helpful way to assess and follow CTD-ILDs. Research examining this possibility is warranted.

### Compliance with ethical standards

**Disclosures** None.

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