Early Pulmonary Involvement of Anti-CADM-140 Autoantibody-positive Rapidly Progressive Interstitial Lung Disease Preceding Typical Cutaneous Symptoms

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Abstract

We herein report a patient with clinically amyopathic dermatomyositis (CADM) who developed anti-CADM-140 autoantibody in association with rapidly progressive interstitial lung disease (RP-ILD). Chest high-resolution computed tomography (HRCT) revealed early pulmonary involvement preceding typical cutaneous lesions. Primary lesions of patchy peribronchial opacity developed ground-glass opacity and consolidation with architectural distortion and traction bronchiectasis. The possibility of anti-CADM-140 autoantibody-associated RP-ILD should be considered when patchy peribronchial opacity of an unknown cause is visible on chest HRCT.

Key words: anti-CADM-140 autoantibody, clinically amyopathic dermatomyositis, high-resolution chest tomography, rapidly progressive interstitial lung disease


Introduction

Clinically amyopathic dermatomyositis (CADM) is a subset of dermatomyositis defined by the criteria of Sontheimer (1). Patients with CADM can develop rapidly progressive interstitial lung disease (RP-ILD), which has a high mortality rate and a 5-year survival of 35% (2). Additionally, the serum autoantibodies that react with a 140-kDa cytoplasmic protein (CADM-140) in patients with CADM have been strongly associated with poor prognosis in RP-ILD (3). Nakashima et al. also reported that seven out of thirteen patients (54%) with anti-CADM-140 autoantibody developed RP-ILD, six of whom (46%) died of respiratory failure (4). These patients are often resistant to intensive therapy and early treatment with glucocorticoid, cyclophosphamide, calcineurin inhibitors and additional rituximab is required for refractory RP-ILD (5). The early diagnosis of connective tissue diseases (CTD) is difficult, especially for CADM patients, who typically do not present with muscle symptoms. Furthermore, ILD associated with CTD can precede systemic symptoms (6, 7); such cases are referred to as “lung-dominant CTD” (6). The detection of CTD as a primary disease for ILD is therefore challenging. Exploring the characteristics of early pulmonary involvement on chest computed tomography (CT) can be useful for the diagnosis of RP-ILD with anti-CADM-140 autoantibody. We herein report a patient with anti-CADM-140 autoantibody who presented with early RP-ILD preceding typical cutaneous lesions.

Case Report

A 64-year-old woman with no previous medical history presented with cough and slight dyspnea on exertion in November 2011. She had never smoked or inhaled dust as an occupational hazard. The physical examination revealed no cutaneous findings or arthralgia. A chest X-ray (CXR) showed bilateral multiple patchy infiltrations (Fig. 1a). Chest high-resolution computed tomography (HRCT) also revealed...
Figure 1. (a) The chest X-ray showed a bilateral multiple patchy infiltration. (b) Bilateral ground glass opacity developed along with typical cutaneous lesions for dermatomyositis.

Figure 2. (a, b) Chest HRCT showed a patchy peribronchial consolidation at the first visit. (c, d) The subpleural ground glass opacity (GGO) and consolidation, with architectural distortion and traction bronchiectasis centering on the primary lesion, was seen. (e, f) The GGO and consolidation with architectural distortion and traction bronchiectasis is shown.

multiple patchy asymmetrical peribronchial opacities in the upper and lower lobes (Fig. 2a, b). We decided treatment was not necessary and recommended periodic follow-up via CXR.
In late December 2011, she noticed skin eruptions on her fingers and elbows; her facial erythema and exertional dyspnea were concurrently aggravated and she returned to our department in mid-January 2012. A physical examination on admission showed Gottron’s sign, mechanic’s hands (Fig. 3) and erythema with slight scaling over the extensor surfaces of both elbows and knees. Muscle weakness and myalgia were not apparent. Her vital signs showed body temperature: 36.7°C; blood pressure: 130/76 mmHg; heart rate: 84 beats/min; respiratory rate: 16/min; SpO2: 95% (room air). Fine crackles were also audible in both lower lung fields. The laboratory findings indicated a white blood cell count: 6,400/μL; red blood cell count: 423x10^12/μL; hemoglobin: 12.5 g/dL; platelet count: 28.4x10^12/μL; C-reactive protein: 3.2 mg/dL; lactate dehydrogenase: 286 IU/L; creatine kinase: 65 IU/L; aldolase: 3.7 IU/L; serum KL-6: 943 U/mL; surfactant protein D (SP-D): <17.2 ng/mL; and ferritin: 300 ng/mL. A CXR showed worsening bilateral glass opacity (GGO) (Fig. 1b) and chest CT on admission revealed subpleural GGO and consolidation with architectural distortion and traction bronchiectasis centered around the patchy peribronchial infiltration that had been seen in December 2011 (Fig. 2c, d). The pulmonary function test on admission revealed a vital capacity (VC): 1.45 L; %VC: 54.5%; forced expiratory volume in one second (FEV1): 1.14 L; %FEV1: 56.7%; FEV1/FVC: 83.2%; and diffusing capacity of the lung for carbon monoxide/predicted value: 68.6%. The tests for anti-nucleic acid antibody, anti-Jo-1 antibody and other anti-aminocyl transfer RNA synthetase (ARS) antibody, and anti-SSA antibody were all negative. The immunoprecipitation results indicated the presence of anti-CADM-140 antibody.

After admission, steroid pulse therapy (500 mg/day for 3 days) and cyclophosphamide pulse therapy (500 mg/day) were immediately started, followed by 80 mg of methyl prednisolone and 200 mg of cyclosporine (trough level was approximately 170 ng/mL and C2 level was -1,500 ng/mL). Although chest CTs were performed before treatment, they did not indicate whether the ILD stages were early-phase (as in our case) or late-phase. In that study, lower consolidation/GGO patterns predominated in anti-CADM-140 autoantibody-positive ILD, and chest CT images showed peripheral and peribronchovascular consolidation with subpleural localized GGO. These patterns closely resemble our case. Therefore, the patchy bilateral asymmetrical peribronchial opacity observed in this case may represent the involvement of

**Discussion**

A characteristic chest HRCT pattern for the initial stages of anti-CADM-140 autoantibody-positive RP-ILD has not been established, nor, to our knowledge, has the clinical course of a primary RP-ILD lesion preceding typical cutaneous lesions and progressing to devastating terminal pulmonary involvement been reported in the literature. Our patient’s primary lesion showed patchy bilateral peribronchial asymmetrical consolidation with progressing ILD centered on these areas. Diffuse GGO and consolidation with architectural distortion and traction bronchiectasis developed at a later stage, suggesting a diffuse alveolar damage (DAD) pattern.

At her first visit, the patient was only suffering from mild respiratory symptoms. Later, her ILD developed along with cutaneous manifestations. Based on the presence of anti-CADM-140 autoantibodies, this patient was thought to have lung-dominant CTD on the first visit. The term “lung-dominant CTD” is reserved for cases where ILD has a rheumatologic element (specific autoantibodies or histopathological features) but does not meet the criteria for CTD due to a lack of the extrathoracic features required for a definitive diagnosis of CTD (6). In these settings, diagnosing CTD as an etiology of ILD is often difficult. Because anti-CADM-140 autoantibody-positive RP-ILD requires immediate therapy, a means of characterizing the chest HRCT findings to facilitate an early diagnosis would be useful.

Similar HRCT findings of anti-CADM-140 autoantibody-positive RP-ILD as seen in our patient have been previously reported (8, 9). In addition, Tanizawa et al. evaluated HRCT features of 25 DM-ILD patients with (n=12) and without (n=13) anti-CADM-140 autoantibody (10). Although chest CT images showed peripheral and peribronchovascular consolidation with subpleural localized GGO. These patterns closely resemble our case. Therefore, the patchy bilateral asymmetrical peribronchial opacity observed in this case may represent the involvement of the lung. The patient’s respiratory failure progressed until she expired 67 days after admission (Fig. 4).

**Figure 3.** (a) Gottron’s sign on the dorsum of the hands. (b) Mechanic’s hands.

Figure 4. The clinical course. mPSL pulse: methylprednisolone pulse, PSL: prednisolone, CyA: cyclosporine, IVCY: intravenous cyclophosphamide, IVIg: intravenous immunoglobulin, NPPV: non-invasive positive pressure ventilation, PaO₂/FiO₂: partial pressure of arterial oxygen/percentage of inspired oxygen.

It is difficult to interpret what those HRCT findings represent histopathologically. In the setting of ILD, patchy peripheral or peribronchovascular consolidation is typical of organizing pneumonia (OP) (11). However, patients with anti-CADM-140 autoantibody-positive RP-ILD have an extremely poor prognosis, and the chest CT pattern presented in our case is unlikely to have reflected OP. The reticular opacity in CADM patients has been reported to correspond to minimal alveolitis or cellular non-specific interstitial pneumonia (12-14). However, acute deterioration that presents a DAD pattern on chest HRCT occurred, centering on the primary lesion. Hence, the early pulmonary involvement in the present case may have reflected localized DAD which is assumed to have the same pathogenesis as DAD (15). Further research on the pathological evidence of the primary lesion is necessary.

A limited number of case reports and a retrospective study are available to evaluate whether chest CT pattern is predictive of the prognosis. Horai et al. reported an anti-CADM-140 autoantibody-positive ILD case with very similar pulmonary lesions (peripheral and focal consolidation) as seen in our case, and the patient, who presented with mild respiratory impairment, was successfully treated with steroid pulse and immunosuppressive therapy (8). Teruya et al. also reported an anti-CADM-140 autoantibody-positive ILD case with peripheral and peribronchial consolidation which resembles our case. The patient had a slight fever, cutaneous and mild respiratory symptoms, was treated with steroid pulse and immunosuppressive therapy and gradually improved. However, the patient developed respiratory failure and worsening bilateral GGO on chest CT afterward (9). Moreover, in the analysis of 21 anti-CADM-140 autoantibody-positive ILD cases, Tanizawa et al. described that the overall survival of patients with lower consolidation/GGO pattern on chest HRCT (similar to our case) was not significantly different from those with other HRCT patterns, although the 90-day mortality was significantly higher in those with a lower consolidation/GGO pattern (16). Therefore, it may be premature to establish a prognostic prediction using only chest HRCT pattern; the comprehensive clinical information is also necessary.

Other prognostic factors have been suggested. It was reported that in patients with DM-related RP-ILD, the anti-CADM-140 antibody titer before treatment was significantly lower in survivors than non-survivors, and the anti-CADM-140 antibody titer correlated with disease activity (17). In addition, the serum ferritin levels have been shown to correlate with the activity of anti-CADM-140 autoantibody-positive RP-ILD (18). Moreover, the utility of ¹⁸F-fluorodeoxyglucose on positron emission tomography/CT to detect CADM-related ILD with the absence of any respiratory symptoms or changes on chest CT was reported (19), and it might be useful for the early detection and initiation of treatment of CADM-related ILD. In the present case, the anti-CADM-140 antibody titer was not evaluated, but the serum ferritin levels progressively increased despite the strong immunosuppressive therapy, which suggested a poor prognosis.

We herein reported a patient with CADM who had anti-CADM-140 autoantibodies and presented with early-stage RP-ILD preceding typical cutaneous lesions. Our findings suggest that when patchy bilateral asymmetrical peribronchial opacity of unknown cause is detected by chest HRCT, the possibility of early-stage RP-ILD associated with anti-CADM-140 autoantibody should be considered.
The authors state that they have no Conflict of Interest (COI).

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References


