



# Anti-MDA-5 Positive Clinically Amyopathic Dermatomyositis Associated with Rapidly Progressive Interstitial Lung Disease Presenting as Spontaneous Pneumomediastinum

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## Abstract

Spontaneous pneumomediastinum (SPM) is a rare complication of anti-melanoma differentiation-associated protein 5 (MDA5) positive clinically amyopathic dermatomyositis (CADM). Herein, we report an elderly patient presented with cutaneous signs and SPM. Serial workup confirmed the anti-MDA5 positive CADM. Treatment initially included methylprednisolone, cyclosporine, and cyclophosphamide, but recurrence led to the use of rituximab and mycophenolate mofetil, ultimately resolving the pneumomediastinum and stabilisation of the lung functions. This underscores the importance of promptly recognising and managing pneumomediastinum in the context of anti-MDA5 positive CADM-associated rapid interstitial lung disease (RP-ILD).

## Subject Areas

Respiratory Medicine

## Keywords

Interstitial Lung Disease, Pneumomediastinum, Anti-MDA5 Antibody

## 1. Introduction

CADM is a subtype of dermatomyositis with predominant cutaneous lesions and minimal or absent muscle weakness, although laboratory or radiological evidence of myositis can be present. SPM, although rare, can occur in patients with anti-MDA5 CADM. SPM is associated with a prevalence of 2.2% in all myositis cases and a striking mortality rate of 25% within the first month of diagnosis [1] [2]. SPM is an important complication to be aware of as it poses significant challenges in diagnosis and management. Herein, we present a case of SPM in a patient with anti-MDA5 CADM with RP-ILD, highlighting the clinical presentation, diagnostic approach, and management strategies.

## 2. Case Report

A woman in her 60s' with a background history of hypertension and dyslipidaemia presented to the outpatient clinic with complaints of non-pruritic, pinkish rashes over the face, trunk, forearm and hands for 2 years. She also complained of proximal upper and lower limb muscle weakness for the past 6 months. Physical examination revealed facial erythematous rash, shawl sign, telangiectasis, and Gottron's papules. Lung auscultation revealed inspiratory fine crepitations (velcro-like) over both lung bases. Baseline oxygen saturation was 94% on room air. Neurological examination revealed proximal muscle weakness of upper and lower extremities (4/5), with normal muscle tone and intact reflexes. The clinical suspicion of dermatomyositis (DM) with possible ILD was made based on the classical dermatological presentation, proximal myopathy and lung findings.

After her clinic consultation, she was scheduled for admission for further workup. Her chest radiograph showed bilateral reticulation. Pulmonary function test revealed a restrictive ventilatory defect [forced vital capacity (FVC): 1.5 L, 60% predicted, forced expiratory volume at 1 s (FEV1)/FVC; 84% predicted] with a reduction of the diffusion capacity for carbon monoxide (DLCO) of 47% predicted. The initial laboratory findings showed a slightly elevated erythrocyte sedimentation rate of 73 mm/hr and a C-reactive protein of 0.8 mg/L. Creatine kinase (33 U/L) was within normal limits, and no myopathic abnormalities were observed on electromyography. Her full blood count and renal, liver and thyroid function were all normal and viral serologies were negative. The tumour markers were negative.

However, due to the low-grade fever and persistent cough, she underwent bronchoalveolar lavage. Bronchoscopy revealed normal findings, and analysis of the bronchoalveolar lavage fluid showed negative results for mycobacterium tuberculosis Gene-Xpert, pneumocystis carinii polymerase chain reaction, bacterial culture, and fungal culture. The autoimmune panel and myositis workup revealed a positive antinuclear antibody with a titre of 1:320 and a positive anti-MDA5 antibody.

On the third day of admission, she experienced sudden subcutaneous emphysema over the chest. An immediate chest computed tomography (CT) showed an

extensive pneumomediastinum with a non-specific interstitial pneumonitis pattern (**Figure 1(A)**). Subsequently, a diagnosis of clinically amyopathic dermatomyositis (CADM) with RP-ILD complicated by SPM was made.

She received high doses of methylprednisolone (five pulses of 1000 mg/day) for 3 days, followed by a tapering regimen of prednisone, starting at 1 mg/kg. As a result, the pneumomediastinum resolved, and she was scheduled for outpatient review in two weeks. Intensive immunosuppressive therapy was considered to induce remission. She began the first cycle of intravenous cyclophosphamide (CP) at 500 mg, in addition to daily steroids.

However, the patient presented to the emergency department three weeks after the first cycle of CP with progressive worsening of shortness of breath and weakness in the limbs. On admission, the patient had no fever and was normotensive. She was hypoxemia with an oxygen saturation of 90% on room air. Physical examination revealed extensive subcutaneous crepitus over the anterior chest wall, extending superiorly to the neck. A chest radiograph showed pneumomediastinum and extensive subcutaneous emphysema, which was confirmed by a subsequent high-resolution CT scan of the thorax (**Figure 1(B)** & **Figure 1(C)**).

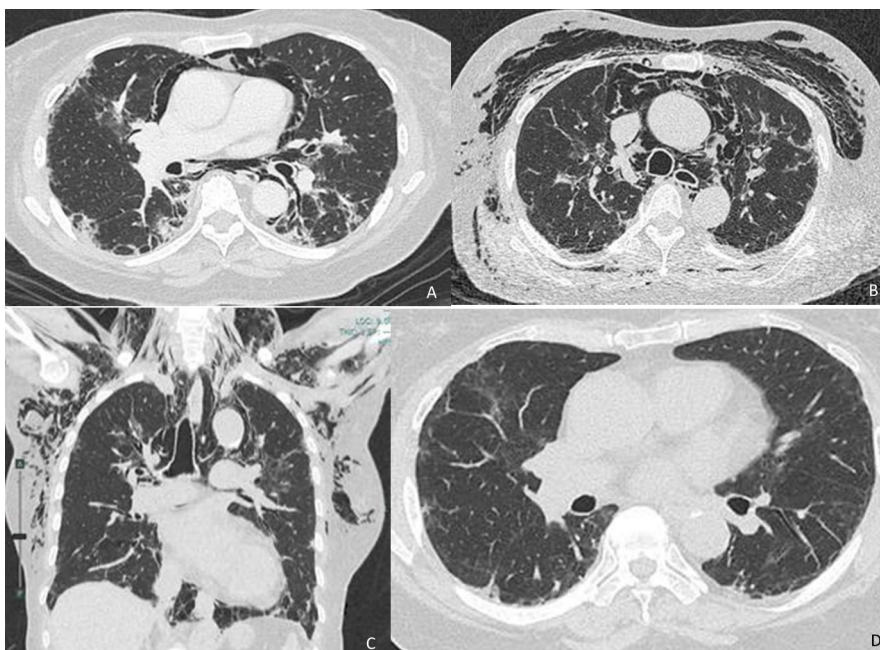
Treatment involved high-flow oxygen therapy to maintain oxygen saturation above 95%. She was pulsed with high-dose methylprednisolone (500 mg per day for 3 days) followed by a tapering regimen alongside cyclosporine A (25 mg twice a day, increase later to 50 mg twice a day). Additionally, the patient received a second cycle of intravenous CP approximately one month after the initial cycle, with plans for biweekly administration after that.

After her third cycle of CP, she developed thrombocytopenia (platelet count  $90 \times 10^9$  L). Consequently, her immunosuppressive regimen was changed to Rituximab. She received two cycles of Rituximab infusion, administered biweekly at a dosage of 1000 mg each. Mycophenolate mofetil (MMF) was added and increased to 1.5g twice daily, and a gradual tapering of oral steroids was continued.

At follow-up 6 months after completing immunosuppressive therapy with cyclophosphamide and rituximab, her functional status (mMRC 1) and pulmonary function test were improved. This was evident from the increase in FVC from 1.5 L to 1.97 L, with an increase in DLCO from 46% to 56% predicted. Her cough, dyspnea and muscle strength were improved. The repeated High-resolution computed tomography (HRCT) thorax showed resolution of the pneumomediastinum with a stable NSIP pattern (**Figure 1(D)**). Her medication regimen continues with a daily dose of 5 mg of prednisone and MMF at 1.5g twice a day.

### 3. Discussion

SPM is characterised by the appearance of free air in the mediastinum, which is not preceded by trauma, surgery, or other medical procedures. It is a rare yet potentially serious complication encountered in DM and may be fatal [2]. In the context of CADM, particularly in cases positive for anti-MDA-5 antibodies, pneumomediastinum presents a unique clinical hurdle [3].



**Figure 1.** (A) CT demonstrated extensive pneumomediastinum with ground-glass opacities predominantly peripheral in pattern with peribronchovascular distribution. (B-C) CT shows extensive pneumomediastinum and subcutaneous emphysema. (D) CT shows interlobular fine septal thickening at bilateral lung bases with associated bronchovascular bundle thickening and traction bronchiolectasis.

Although the exact mechanisms causing pneumomediastinum in CADM remain unclear, various theories have been postulated. One prominent theory suggests that the rupture of subpleural blebs and cysts formed due to the consequence of interstitial fibrosis in CADM may play a significant role. Furthermore, it's hypothesized that elevated pulmonary pressures and inflammation could also be contributing factors, leading to damage to the alveoli and subsequent leakage of air into the mediastinum, resulting in pneumomediastinum [4]. Moreover, anti-MDA-5 antibodies, recognized for their association with more severe ILD manifestations, could exacerbate lung damage through endothelial cell damage, compromised angiogenesis, and irregular cytokine production. Understanding these pathophysiological processes is imperative for guiding treatment strategies and enhancing patient outcomes [5].

Diagnosing pneumomediastinum in anti-MDA-5 ADM can pose a challenge due to overlapping clinical features with other respiratory conditions and the rarity of the complication. Imaging modalities play a key role in confirming the diagnosis and evaluating the extent of mediastinal involvement in CADM patients. Chest X-ray is often employed as an initial diagnostic tool, revealing characteristic findings of “continuous diaphragm sign” or “Macklin effect.” which are seen as linear streaks of air outlining mediastinal structures. HRCT of the thorax offers higher sensitivity and specificity for detecting pneumomediastinum and assessing its severity. HRCT thorax provides detailed anatomical information on the extent and distribution of air in the mediastinum. It can also help identify underlying

lung pathology, such as interstitial lung disease or pneumothorax, which may contribute to pneumomediastinum. Integration of radiological findings with clinical presentation is crucial for accurate diagnosis and treatment planning [6].

Early recognition and prompt initiation of management of pneumomediastinum is the key to preventing adverse outcomes and optimising patient survival. The management approach for pneumomediastinum in anti-MDA-5 CADM with RP-ILD is primarily supportive, focusing on symptom relief and addressing underlying lung pathology. Supportive measures include oxygen supplements and analgesics to improve respiratory comfort. Vigilant monitoring for any signs of respiratory compromise is crucial to recognise severe cases that require admission to the intensive care unit. When ILD and respiratory failure progress, pulse corticosteroid therapy may be required.

The first-line treatment approach for anti-MDA5 CADM patients with RP-ILD involves administering a glucocorticoid along with either a calcineurin inhibitor (such as cyclosporine or tacrolimus) or a triple therapy regimen that includes intravenous cyclophosphamide alongside the other two medications [7] [8]. For patients unable to tolerate calcineurin inhibitors, alternative immunosuppressants like MMF or biologic therapies such as the anti-CD20 humanised monoclonal antibody rituximab should be considered [9]-[11]. Other drugs or biological therapies, including basiliximab or tofacitinib, have also shown promising results. For refractory cases, it's reasonable to consider adding another immunosuppressive drug to their current treatment or switching to a different immunosuppressant.

#### **4. Conclusion**

SPM is a rare but potentially life-threatening complication of CADM, particularly in patients positive for anti-MDA-5 antibodies. Optimising diagnostic approaches and implementing multidisciplinary treatment strategies are essential for effectively managing the pneumomediastinum and improving outcomes.

#### **Author Contribution Statement**

The work conducted and presented in this manuscript has not been published or submitted for publication in another journal. All authors named in the manuscript have made substantial contribution each to qualify for authorship according to BIMJ authorship criteria and have approved of the content of the manuscript. We have disclosed all financial support for our work and other potential conflicts of interests.

#### **Ethics Statement**

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

#### **Conflicts of Interest**

The authors declare no conflicts of interest.

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