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# Macrophage activation syndrome and rapidly progressive lung disease as life-threatening manifestations of anti-MDA5 antibody disease. A case report

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## Abstract

Anti-melanoma differentiation-associated protein 5 (MDA5) antibody-positive syndrome is a severe condition classified among the idiopathic inflammatory myopathies associated with rapidly progressive interstitial lung disease (RP-ILD). The present case report describes a complex patient with RP-ILD in the context of anti-MDA5-positive dermatomyositis (DM). The patient showed severe lung and skin manifestations involving hands, arms, and face, and the disease was first complicated by acute renal failure and then by macrophage activation syndrome (MAS). Finally, infectious risk delayed an effective treatment, probably increasing the rapid progression of lung involvement. A pathogenetic link between DM and MAS has been recently suggested; anti-MDA5 positive patients present higher serum soluble CD163 levels, which is a scavenger receptor for the hemoglobin/haptoglobin complex expressed on macrophages and a marker of macrophage activation in various conditions, including MAS. The patient has been treated according to the American College of Rheumatology/American College of Chest Physicians guidelines, adapting the strategy to his infectious complications. Beyond the complex clinical picture and treatment strategy, this case highlights the challenging decision-making process involved in the management of acute respiratory failure in patients with acute exacerbation of interstitial lung disease. The patient underwent helmet non-invasive ventilation (NIV), with a favorable clinical response. Helmet NIV has demonstrated advantages over mask interfaces, including better patient comfort, reduced air leaks, and more consistent delivery of positive end-expiratory pressure. These features contribute to lower inspiratory effort and improved clinical outcomes, including reduced intubation and mortality rates. In conclusion, patients with anti-MDA5 antibody disease need a multidisciplinary approach, including expert rheumatologists, pulmonologists, and radiologists for both monitoring and disease management.

**Key words:** idiopathic inflammatory myopathies, interstitial lung disease, anti-MDA5, macrophage activation syndrome.

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## Introduction

Anti-melanoma differentiation-associated protein 5 (MDA5) antibody-positive syndrome is a severe condition classified among the idiopathic inflammatory myopathies, clinically characterized by cutaneous and muscular manifestations of dermatomyositis (DM). For the high occurrence of rapidly progressive interstitial lung disease (RP-ILD), anti-MDA5 syndrome is considered a potentially life-threatening condition (1).

## Case Report

In May 2024, a 55-year-old man referred to our center with a degree 1 exertional dyspnea according to the modified Medical Research Council scale for dyspnea (2), and muscle weakness over the last month. His medical history was positive for smoking, arterial hypertension, and steatosis. In 2021, he was hospitalized because of respiratory failure due to COVID-19 interstitial pneumonia, treated with remdesivir and non-invasive mechanical ventilation (NIV). After resolution, no lung fibrosis was detected at chest high-resolution computed tomography (HRCT).

A chest HRCT performed in May 2024 showed diffuse subpleural, bilateral ground-glass opacities (GGO), particularly in the lower and medium lobes, with initial lung fibrosis. After 4 weeks of prednisone (10 mg/daily), a new HRCT showed worsening of the previous alterations, especially fibrotic ones. Physical examination showed "velcro-type" crackles on chest auscultation and erythematous-desquamative papules on the fingers, namely Gottron papules.

Lung function tests (LFTs) showed a predicted forced vital capacity (FVC) of 68% (2.94 L), and a moderately reduced single-breath diffusing capacity of the lung for carbon monoxide (DLCO) (46% of predicted); the 6-minute walking test (6MWT) showed a severe desaturation at minute 6 [pulse oximetry saturation ($SpO_2$) 90%]. Bronchoalveolar lavage (BAL) detected a few DNA

sequences of *Pneumocystis jiroveci* and a mild increase of *Aspergillus galactomannan* (index 0.47, positive if >0.4). After the procedure, a transient respiratory failure was reported. Laboratory tests showed increased liver function tests, erythrosedimentation rate, and creatine kinase (225 U/L); β-D-glucan was negative. Finally, autoimmunity screening revealed positivity for anti-MDA5 antibodies.

Videocapillaroscopy showed a scleroderma pattern, with enlarged bushy capillaries, architectural disarrangement, and a mild capillary loss.

High-dose corticosteroids (prednisone 40 mg/daily) were started with improvement of both dyspnea and weakness, together with peripheral oxygenation. Meanwhile, the case was discussed in our multidisciplinary team (MDT), including a pulmonologist, rheumatologist, and chest radiologist. The MDT confirmed the diagnosis of anti-MDA5 syndrome and proposed treatment with rituximab and corticosteroids, and concurrent cotrimoxazole prophylaxis. However, the patient asked for delaying anti-CD20 therapy for the supposed risk of infection.

After 2 weeks, he was admitted to the Piacenza hospital because of acute renal failure with hyperkalemia and metabolic acidosis with elevated lactate serum and transaminases levels, and thrombocytopenia. C-reactive protein was normal. Renal failure was ascribed to dehydration and drug toxicity, mainly related to cotrimoxazole and furosemide, and recovered in a few days. However, laboratory tests showed persistent thrombocytopenia and lymphocytopenia in association with high ferritin (4795 ng/mL, normal 12-300 ng/mL) and triglyceride values (352 mg/dL, normal 50-170 mg/dL). Bone marrow biopsy showed a reduced cell count, slight lymphoplasmacytosis, changes in erythro- and megakaryocytopoiesis, together with hemophagocytosis suggestive of macrophagic activation syndrome (MAS). Intravenous high-dose corticosteroid treatment (1 g for 3 days and then 1 mg/kg daily) was started, with improvement of blood count.

In a few days, fever and acute hypoxemic respiratory failure occurred, with rapidly progressive respiratory distress. A chest HRCT showed diffuse bilateral consolidations with GGO, suggesting an acute exacerbation (AE) of ILD. The patient was transferred to the University Hospital of Modena.

Here, high-dose intravenous corticosteroids were administered, first methylprednisolone 500 mg for 3 days, then 1 mg/kg, associated with intravenous immunoglobulins (IVIg) (2 g/kg in 4 days) and antibiotic therapy with piperacillin/tazobactam.

The day after, BAL was performed, which identified cytomegalovirus (CMV) (29,000 copies). Due to this finding, along with the detection of viraemia, antiviral therapy with ganciclovir was initiated.

Dyspnea and desaturation appeared a few hours after the BAL. A chest X-ray revealed an increase in lung abnormalities, with bilateral pulmonary consolidations, more evident in the middle-to-lower right lung fields. NIV with a helmet interface was initiated (positive end-expiratory pressure 12 cmH2O, pression support 12, fraction of inspired oxygen 40%), along with mild sedation.

In the subsequent days, clinical and radiological improvement was achieved, leading to the discontinuation of NIV and a transition to high-flow nasal cannula.

On August 9th, a new chest HRCT confirmed the presence of consolidative areas with GGO appearance, partially confluent and partly solid, along with reticulonodular thickening of the interlobular septa. The antero-apical regions of both upper lobes were relatively spared. Additionally, bilateral pleural effusions were noted, with a maximum thickness of 3 cm. Following a new multidisciplinary evaluation of the case, treatment with rituximab, 1 g every other week, was started. During the following days, the patients improved, and a chest X-ray showed significant resolution of GGO and complete resolution of the bilateral pleural effusions.

After 3 weeks, the patient was discharged with home oxygen therapy at 1 L/min at rest and 3 L/min during exertion, along with prednisone 50 mg daily. The corticosteroid dose was tapered to 12.5 mg/daily in 2 months.

At the follow-up visit in November 2024, the patient reported overall well-being, with a progressive recovery of everyday and sports activities. Resting $SpO_2$ on room air was 93%. LFTs showed a moderate restrictive ventilatory defect (FVC 55%) and a severe reduction in DLCO (34%). Minimal non-infiltrated Gottron's papules and mechanic's hands were reported at physical examination.

A new chest HRCT demonstrated radiological improvement, with significant reduction of the parenchymal consolidations, particularly in the upper lobes, although an irregular reticular involvement of the peripheral and basal parenchyma persisted. Corticosteroids were gradually reduced to 5 mg daily of prednisone.

In February 2025, the patient reported occasional exertional dyspnea that did not impair daily activities. Resting $SpO_2$ in room air was 96%. Physical examination revealed relapse of Gottron's papules on the hands. LFTs remained stable compared to previous assessments (FVC 51% *vs*. 55%, DLCO 34% *vs*. 34%, 6MWT 400 m *vs*. 340 m) (Figure 1).

A new course of rituximab was repeated, while corticosteroids and trimethoprim-sulfamethoxazole prophylaxis, as well as oxygen supplementation during exertion, remained unchanged.

Despite the stability of lung function, as a consequence of the severe pulmonary involvement, the patient was referred for evaluation for lung transplantation.

## Discussion and Conclusions

We have described a complex patient, characterized by many negative prognostic factors, other than anti-MDA5 antibodies. In fact, he showed severe lung and skin manifestations, involving hands, arms, and face; the disease was first complicated by acute renal failure and then by MAS. Finally, infectious risk delayed an effective treatment, probably increasing the fast progression of the lung involvement.

Clinical history of our patient was complicated by the occurrence of MAS, a life-threatening hyperinflammatory syndrome linked to aberrant activation of lymphocytes and macrophages and overproduction of pro-inflammatory cytokines. The clinical picture is defined by a variety of symptoms, such as spiking fever, splenohepatomegaly, cytopenia, coagulopathy, hyperlipidemia, and hyperferritinemia (3).

In rheumatic patients, MAS is frequently described as a complication of systemic juvenile idiopathic arthritis, adult-onset Still's disease, systemic lupus erythematosus, and even DM, including juvenile forms. Although MAS is a rare complication in adult DM, it is a well-known risk factor for mortality (3). A possible link between anti-MDA5-positive DM and MAS is currently debated, and a pathogenetic connection has been recently suggested (4).

Type I interferon (IFN-I) and interferon-stimulated genes are positively regulated in patients with anti-MDA5 anti-MDA5 positive DM. IFN-I can drive macrophage activation in multiple

ways, including the stimulation of monocytes and tissue macrophages, inducing a proinflammatory state. Activated macrophages, particularly in inflammatory conditions like MAS, release serum soluble CD163 (sCD163) into the circulation (5, 6). Anti-MDA5 positive patients have significantly higher sCD163 levels (6), which is a scavenger receptor for hemoglobin/haptoglobin complex expressed on macrophages, and a marker of macrophage activation in various conditions, including MAS (7). Alternatively, anti-MDA5 antibodies can support the inflammatory process, generating a cytokine storm, a downstream explosion of pro-inflammatory cytokines which amplifies macrophage activation, leading to further shedding of sCD163 into the blood (6-10). The elevation of sCD163 levels in anti-MDA5 positive patients appears to be the result of macrophage activation driven by both IFN I signaling and downstream cytokine storm mechanisms (6-10). In the above-described case report, we cannot exclude a possible role of CMV infection as a further trigger for MAS. In particular, we cannot discriminate between CMV

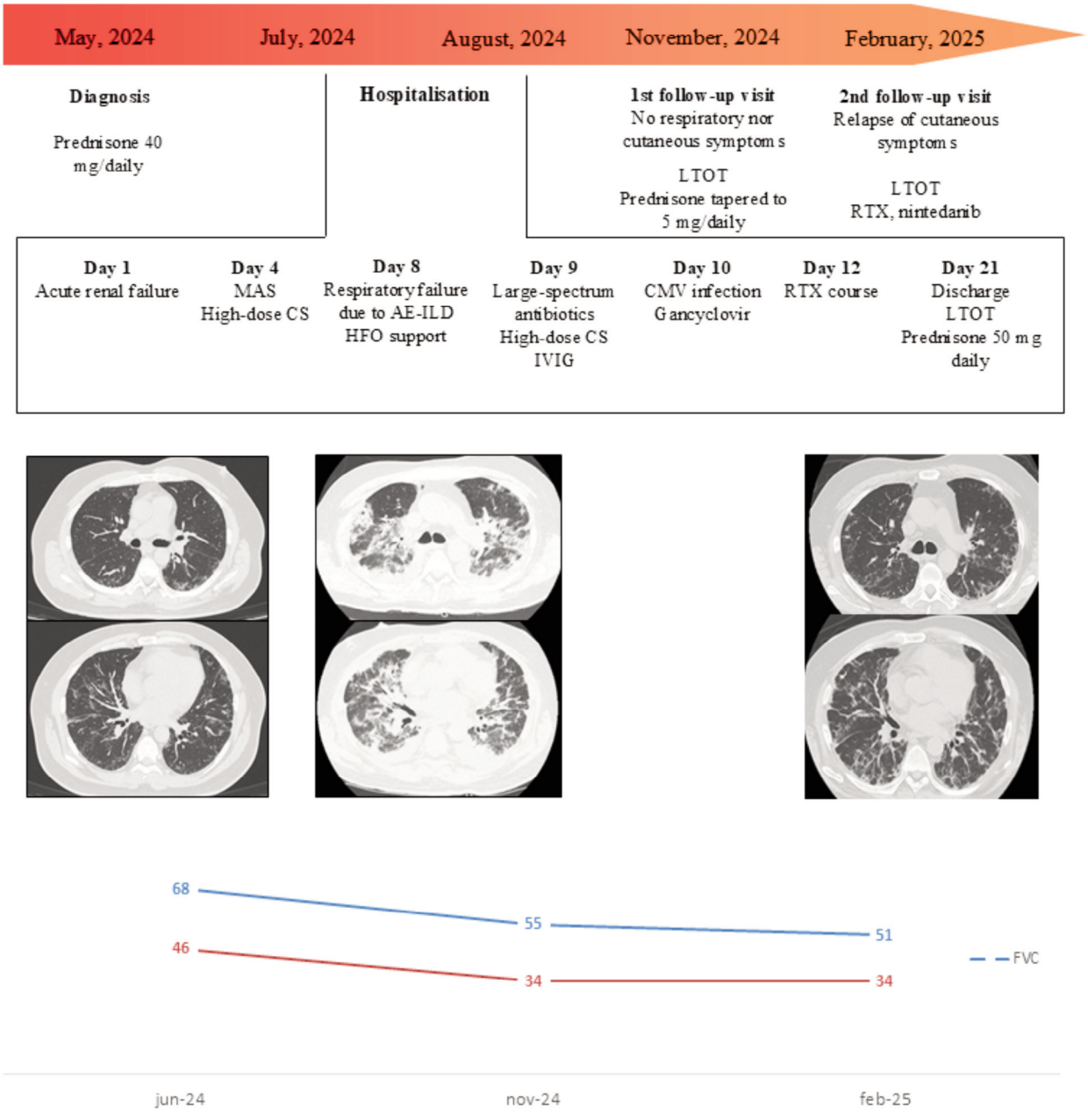


**Figure 1.** Clinical and functional evolution of the patient. AE-ILD, acute exacerbation of interstitial lung disease; CS, corticosteroids; MAS, macrophage activation syndrome; HFO, high flow oxygen; RTX, rituximab; NIV, non-invasive ventilation; IVIg, intravenous immunoglobulins; LTOT, long-term oxygen therapy; LFTs, lung function tests; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.

reactivation in the setting of the patient's DM complicated with MAS or CMV reactivation as an independent trigger of MAS (11).

Mortality of MAS is high, more than 30% of patients in some case-series, and the prognosis is negatively affected by the presence of anti-MDA5 (8). The diagnostic process is difficult due to a lack of diagnostic criteria and to possible similarity between symptoms of MAS and DM (10, 12).

The treatment of MAS requires removal of known triggers, supportive care measures in case of life-threatening presentation, and immunosuppressive therapy. In DM patients complicated by MAS, treatment schedules include high-dose corticosteroids in combination with IVIg, and immunosuppressants such as cyclosporine, cyclophosphamide, and Janus kinase inhibitors (9, 10). Our patient experienced MAS 2 months after the onset of anti-MDA5-positive DM. In a recent retrospective study, MAS occurred early in anti-MDA5 patients, within 3 months of diagnosis, mainly in patients with skin involvement, namely heliotrope sign, Gottron's papule, and V-neck sign (12). Moreover, no difference was observed regarding the prevalence of RP-ILD after MAS, but deceased patients had a higher rate of RP-ILD than survivors (12).

Our patient has been successfully treated according to the recent American College of Rheumatology/American College of Chest Physicians guidelines for the treatment of systemic autoimmune rheumatic disease-related ILDs in a multidisciplinary setting (13, 14). In resistant or severe cases, guidelines recommend a triple combination treatment including IVIg, other than corticosteroids and immunosuppressants (13).

Considering the concurrent CMV viraemia and the risk of infection, we decided to add IVIg, rather than an immunosuppressant, as first-line treatment in combination with corticosteroids; rituximab was added as soon as we observed a reduction in CMV viraemia. Although treatment choice may depend on disease severity, comorbidities, and infectious risk, rituximab is usually suggested as the first choice, followed by other immunosuppressants (13).

Finally, this case highlights the complex decision-making process involved in the management of acute respiratory failure in patients with acute exacerbation of ILD (AE-ILD), particularly following diagnostic procedures such as BAL. Despite the known association between mechanical ventilation and an increase in in-hospital mortality in the setting of AE-ILD (15), NIV was successfully employed in this patient. Several factors supported the use of NIV. First, chest HRCT did not demonstrate features consistent with a usual interstitial pneumonia (UIP), which has been associated with poor outcomes and increased susceptibility to ventilator-induced lung injury due to the underlying architectural distortion and mechanical vulnerability of the fibrotic lung (16). Instead, imaging revealed bilateral GGO and confluent consolidations, suggesting a potentially reversible inflammatory process rather than advanced fibrosis. Second, the patient exhibited markedly elevated inspiratory effort, as quantified by nasal manometry, underscoring the physiological need for ventilatory unloading. Due to these findings, NIV was initiated *via* a helmet interface, in combination with low-dose dexmedetomidine to improve tolerance and synchrony (17). Helmet NIV has demonstrated advantages over mask interfaces, including better patient comfort, reduced air leaks, and more consistent delivery of positive end-expiratory pressure. These features contribute to lower inspiratory effort and improved clinical outcomes, including reduced intubation and mortality rates. The use of mild sedation with dexmedetomidine further enhanced patient comfort and compliance with NIV. The clinical response was favorable, with the resolution of respiratory distress and stepwise de-escalation of support from NIV to high-flow oxygen therapy and ultimately to low-flow nasal cannula. This outcome confirms that NIV may be a viable and effective intervention in selected AE-ILD cases, particularly those lacking radiological evidence of UIP and exhibiting significant inspiratory effort. Nevertheless, team expertise is crucial when assessing a targeted approach based on radiological, physiological, and clinical parameters to guide the optimal selection of respiratory supports for these patients. While caution remains warranted due to the potential risks associated with mechanical ventilation in this population, this phenotype-driven approach may expand the therapeutic window for non-invasive strategies in carefully selected patients.

In conclusion, patients with anti-MDA5 antibody disease need a multidisciplinary approach, including an expert rheumatologist, pulmonologist, and radiologist for both monitoring and disease management. The disease, mainly ILD, can show a rapid progressive course, and life-threatening complications can be unpredictable. In these cases, treatment becomes challenging and the prognosis severe; therefore, an early referral for lung transplant might be suggested.

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