Case Report

A 72-year-old man with acute lung injury and anti-melanoma differentiation-associated gene 5 antibody: A case report

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ARTICLE INFO

ABSTRACT

Anti-melanoma differentiation-associated gene 5 antibody (anti-MDA-5 Ab) is associated with amyopathic dermatomyositis (DM). These patients are particularly at high-risk for developing acute and rapidly progressive interstitial lung disease (ILD). Given the lack of muscle-related symptoms, along with its sudden onset and rapid clinical progression, the diagnosis of anti-MDA-5 Ab + ILD represents a challenge for clinicians. Even after the diagnosis is established, prognosis remains dismal owing to a hyperinflammatory state, mimicking cytokine storm, commonly refractory to potent immunosuppressive therapy. Hence, we present an elderly African American man who developed acute and rapidly progressive ILD in the setting of positive anti-MDA5 Ab, in whom lung histopathology was consistent with organizing phase of diffuse alveolar damage. Despite receiving combined immunosuppression with corticosteroids, cyclosporine, and cyclophosphamide, he developed irreversible lung injury within a month and was eventually referred for lung transplant evaluation.

1. Introduction

Interstitial lung diseases (ILDs) are a broad spectrum of diseases affecting the lung parenchyma sometimes associated with connective tissue diseases (CTDs) [1]. ILDs can be the first (and only) clinical manifestation of CTDs, such as dermatomyositis (DM), where the appearance of classic skin and muscle findings may be delayed by several months or years [1]. Of particular interest, patients with amyopathic DM, characterized by the lack of muscle involvement, are at higher risk for developing acute and progressive ILD [2].

The association between anti-melanoma differentiation-associated gene 5 antibody (anti-MDA-5 Ab) and amyopathic DM was first described in 2005. Since then, several ILD phenotypes, including organizing pneumonia (OP), non-specific interstitial pneumonia (NSIP), and acute interstitial pneumonia (resembling diffuse alveolar damage [DAD]) have been described in patients with anti-MDA-5 Ab + lung disease [3,4].

The presence of anti-MDA-5 Ab in patients with ILD is of utmost therapeutic and prognostic relevance. Due to immune system hyperactivation and cytokine storm triggered by anti-MDA-5 Ab, empiric immunosuppressive regimens, often consisting of multiple and

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potent immunosuppressive drugs, are indicated [4,5]. Unfortunately, these patients often have refractory disease, and their prognosis remains poor [6].

Hereby, according to case report (CARE) guidelines [7], we describe the case of a 72-year-old African American man who developed acute and rapidly progressive ILD, within a period of weeks, in the setting of positive anti-MDA-5 antibody. A lung tissue biopsy revealed scattered areas of organizing phase of DAD. His lung disease was refractory to a combined immunosuppressive regimen consisting of corticosteroids, cyclosporine, and cyclophosphamide, and he was eventually referred for lung transplant evaluation.

2. Case report

A 72-year-old African American man presented to the emergency department (ED) with progressive dyspnea within the last month. His dyspnea was first apparent only on exertion and progressed to rest. He was a former smoker of 10 pack-years. Four weeks before the current presentation, he was admitted to a local university hospital due to Influenza-A infection complicated by presumed bacterial pneumonia and was treated with oseltamivir and a course of systemic antibiotics. At that time, a chest computed tomography (CT) revealed mild emphysematous changes in the upper lobes, in addition to confluent lower lobe opacities (right greater than left) consistent with multifocal pneumonia (Fig. 1).

On arrival to our institution, he was in acute distress; tachycardic with a heart rate of 100 beats per minute, tachypneic with a respiratory rate of 30 per minute, and hypoxemic with an oxygen saturation in the low 80s that improved to more than 90 % with 6L/min of oxygen supplementation. His body mass index was 18 kg/m^2. His physical examination was remarkable for scaphocephalic head shape, loss of muscle mass, and inspiratory crackles in bilateral lung fields. Of note, the patient was a suboptimal historian and lacked social support; therefore, further details about his current symptoms and collateral information were missing. A chest CT angiography ruled out pulmonary embolism but revealed upper-lobe predominant honeycombing, traction bronchiectasis, and diffuse
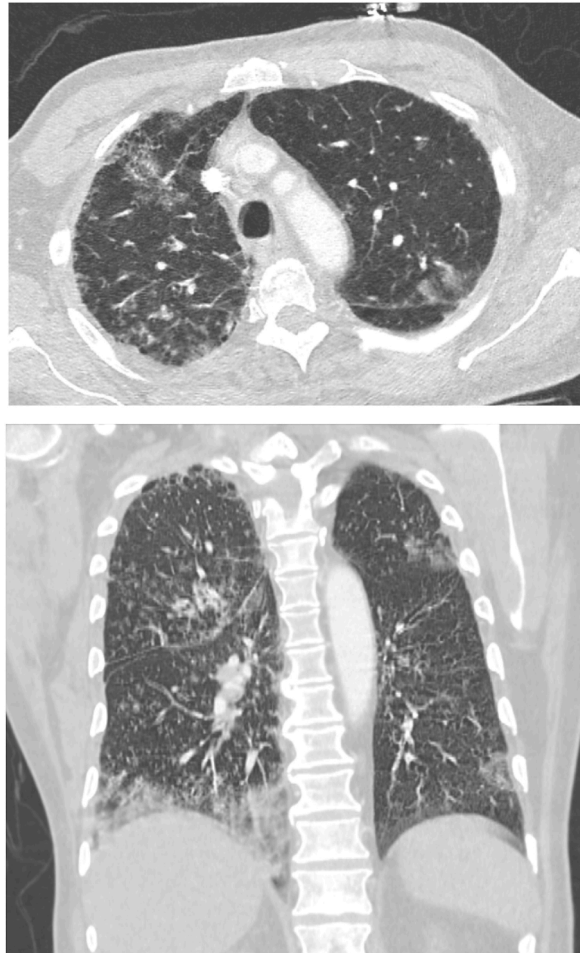

Fig. 1. (A and B). Chest CT from outside hospital (one month prior to admission). **A**- Axial slides showing mild to moderate emphysematous changes of the right upper lobe. **B**- Coronal slides showing severe diffuse airway inflammation and impaction. Confluent airspace opacification of the right greater the left lower lobes. Findings of severe bronchiolitis and dependent bronchopneumonia in the right greater than left lower lobes, probable components of aspiration and infection. Reactive multistation mediastinal and hilar lymph nodes.

bilateral ground glass opacities (Fig. 2). Initial laboratory analysis demonstrated normal blood cell counts, elevated C-reactive protein (CRP) concentration (100.3 mg/L, normal 0–5), erythrocyte sedimentation rate (ESR) (88 mm/1hr, normal <20), and brain natriuretic peptide (230 pg/ml, normal 0–100). Serum procalcitonin, creatinine, and creatinine kinase (CK) concentrations were normal. An extensive viral respiratory panel, urine legionella antigen, human immunodeficiency virus, and antinuclear antibody screening were negative (Table 1).

The patient was admitted to the progressive care unit for further work-up. At this point, pulmonary infections, cardiogenic pulmonary edema, pulmonary hemorrhage, and rapidly progressive interstitial lung disease were considered part of the differential diagnoses. One day after admission, a transthoracic echocardiogram showed a normal left ventricular ejection fraction of 60 % and low estimated right atrial pressure (~3 mmHg), ruling out cardiogenic pulmonary edema. Blood cultures remained negative after 48 hours, and infections were deemed to be less likely.

Pulmonary medicine was consulted, and the patient was initiated on corticosteroid therapy as empirical treatment for acute exacerbation of clinically suspected hypersensitivity pneumonitis due to upper lobe predominance of interstitial lung disease. He was started on IV methylprednisolone 1mg/kg within 24 hours. Three days later, the patient developed worsening hypoxemic respiratory failure and required endotracheal intubation and initiation of mechanical ventilation. His oxygen requirements remained elevated and serial chest radiographs revealed no improvement despite following lung protective ventilation protocol. Given the growing concern for acute ILD flare, the patient received intravenous immunoglobulin 60 g for two consecutive days without improvement.

Ten days after admission, a bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial cryobiopsy (TBLC) was performed after being postponed for several days owing to the patient's high oxygen requirements. The clinical expertise of the interventional pulmonologist at our institution made this feasible despite the use of 100 % fraction of inspired oxygen (FiO$_2$) and positive end-expiratory pressure (PEEP) of 16 cm H$_2$O. The airways were normal upon inspection, and minimal amounts of secretions were visualized; BAL analysis revealed a white blood cell (WBC) count of 96 c/cmm with 60 % neutrophil, 37 % macrophages, and 3 % lymphocytes. Gram stain and cultures from BAL were negative. Pathology results showed an organizing phase of DAD (Fig. 3).

Eventually, an extensive autoimmune work-up revealed an elevated concentration of anti-MDA-5 Ab, while antinuclear antibody, rheumatoid factor, anti-synthetase, anti-cyclic citrullinated peptide, anti-topoisomerase-I, and other autoantibody titers were normal
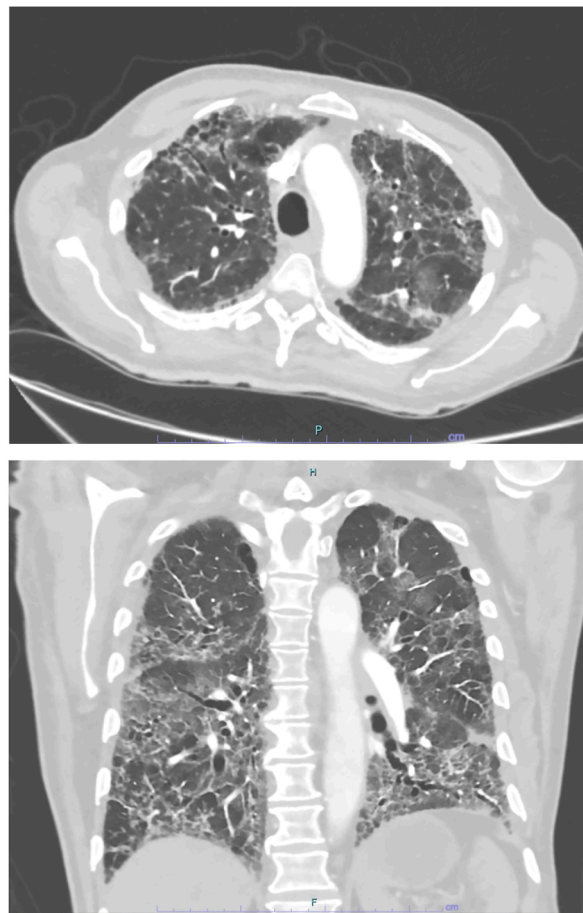

Fig. 2. Chest CT at the time of admission. **A-** Axial slides showing honeycombing with associated traction bronchiectasis in bilateral upper lobes. **B-** Coronal slides showing Diffuse bilateral groundglass opacities with upper lobe predominance and superimposed moderate to severe centrilobular and paraseptal emphysema.

Table 1
Laboratory data from admission date, day 3 (peri-intubation), and day 10 (peri-bronchoscopy).

Variables	On admission	Day 3	Day 10
Blood cell counts			
White blood cell count (x 10^3/mcL)	7.1	13.9	9.7
Hemoglobin (gm/dL)	13.4	9.4	7.5
Platelet count (x10^3/mcL)	339	298	217
Serum chemistry			
Creatinine (mg/dL)	0.66	0.54	0.56
Blood urea nitrogen (mg/dL)	18	14	25
C-reactive protein (mg/L)	100.3	–	–
Erythrocyte sedimentation rate (mm/1h)	88	–	–
Procalcitonin (ng/mL)	0.26	–	–
Brain natriuretic peptide (pg/mL)	230.6	–	–
Troponin-I (ng/mL)	0.04	0.02	–
Lactic acid (mmol/L)	2.4	2.8	2.5
Blood gases			
pH	7.54	7.28	7.42
pO2	–	162	104
FiO2	–	100	60
pCO2	33	57	63
Respiratory viral panel (including influenza-A and B, Parainfluenza, Coronaviruses, Respiratory syncytial virus, Adenovirus, and SARS-CoV2)	–	Negative	–
HIV testing	Negative	–	–
BAL fluid			
White blood cell count	–	–	96
Neutrophils (%)	–	–	60
Lymphocytes (%)	–	–	3
Monocytes (%)	–	–	37
Red blood cell count	–	–	9400
Autoimmune panel			
Anti-nuclear antibody	–	–	Negative
Anti-Rheumatoid factor	–	–	Negative
Anti-cyclic citrullinated peptide	–	–	Negative
Anti-Scl-70	–	–	Negative
Anti-centromere	–	–	Negative
AntiMDA-5	–	–	Positive (55, normal <11)

(Table 1). The diagnosis of anti-MDA5 Ab-associated rapidly progressive interstitial lung disease was made. He was started on pulse dose steroids with intravenous methylprednisolone 1000mg daily, along with cyclosporine and cyclophosphamide. Unfortunately, the immunosuppressive therapy did not yield significant improvements in the overall clinical condition, and the patient was referred to a lung transplant center for evaluation.

3. Discussion

We presented a patient with acute-onset and rapidly progressive ILD, with histologic features consistent with diffuse alveolar damage, in the setting of positive anti-MDA-5 Ab. Several remarkable findings in this case are worth discussing.

First, a month before admission, the patient had an episode of influenza-A infection complicated with pneumonia. RNA viruses (such as Influenza-A) are sensed by MDA-5 intracellular receptors and are known triggers of MDA-5 antigen overexpression as part of an innate immune system response aimed to clear the viral infection [8]. Due to unclear reasons, MDA-5 antigen overexpression can potentially lead to anti-MDA-5 Ab overproduction, as likely occurred in the present case, triggering a hyperinflammatory cascade resembling cytokine storm responsible for the lung parenchymal injury [9].

Second, our patient was oligosymptomatic and presented only with pulmonary manifestations associated with anti-MDA-5 syndrome, which made the diagnosis challenging. This is not uncommon among anti-MDA-5-Ab + patients, who have a lower tendency to develop myositis and usually present with borderline high- or normal CK concentration, as was noted in our patient. Furthermore, our patient was of African American descent, an ethnic group at increased risk for developing DM, but in whom typical cutaneous manifestations may appear different and are commonly underreported, potentially adding further diagnostic delays [10].

Third, the prevailing histopathological pattern detected in patients with this condition following surgical or bronchoscopic biopsy is DAD. DAD is a histologic pattern of injury that is non-specific to anti-MDA5-Ab syndrome, but that commonly portrays poor prognosis and limited response to corticosteroid therapy [11]. Given the rapid progression of the anti-MDA-5-Ab + ILD, histologic confirmation often relies on post-mortem analysis. However, in our case, we obtained a definitive histologic diagnosis with the performance of TBLC. TBLC is an increasingly used diagnostic modality among ILD patients due to its low rate of periprocedural complications and high diagnostic accuracy [12].
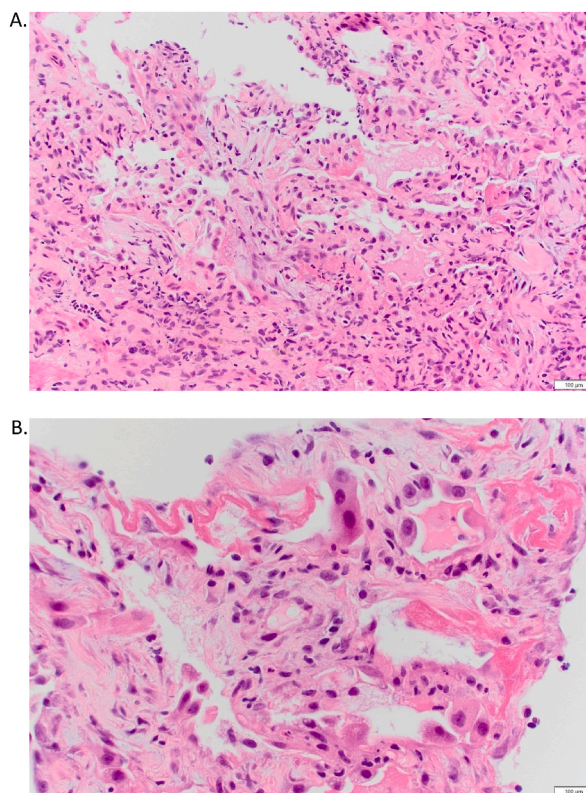
Fig. 3. (A and B). Histopathology obtained by transbronchial cryobiopsy.
Fig. 3A: Hematoxylin and eosin-stained section of the lung cryobiopsy (200X) showing intra-alveolar fibroblast plugs and scant fibrin.
Fig. 3B: Hematoxylin and eosin-stained section of the lung cryobiopsy (400X) with vacuolated reactive pneumocytes adjacent to eosinophilic hyaline membranes.
Microscopic description: Sections from the cryobiopsies showed an organizing phase of injury (Fig. 3A). This was present interspersed with scattered hyaline membranes and markedly reactive and vacuolated pneumocytes (Fig. 3B), consistent with a subacute or organizing phase of acute lung injury/organizing diffuse alveolar damage. Special stain for *Pneumocystis* spp. was negative (not shown).

Lastly, our patient was treated with a combined "triple" immunosuppressive therapy, including a pulse of corticosteroids, a calcineurin inhibitor (cyclosporine), and cyclophosphamide once the diagnosis of anti-MDA-5-associated ILD was established. This approach is supported by a prospective study of 29 patients with anti-MDA-5-Ab + ILD that showed a survival benefit at 6-months follow-up [13]. Unfortunately, the patient showed no clinical or imaging improvement and was referred to a lung transplant center for evaluation. For refractory disease, other agents such as Tocilizumab (anti-IL-6 receptor antagonist) have been described in small series as a salvage therapy alternative after unsuccessful triple immunosuppressive regimen [14]. In more stable patients, further therapies, including selective Janus kinase inhibitors, such as tofacitinib, aimed to target the hyperinflammatory cascade, and antifibrotic therapy, such as pirfenidone, aimed to reduce the rapid collagen deposition in the lungs, have shown promising results [15,16].

In summary, anti-MDA-5-Ab + ILD is a challenging diagnosis and portrays a highly adverse clinical outcome. Further research is mandated to improve the diagnostic yield and optimal therapeutic strategy.

Funding source

CRediT authorship contribution statement

Irakli Lemonjava: Writing – original draft, Writing – review & editing. **Jose Manuel Martinez Manzano:** Supervision, Writing – original draft, Writing – review & editing. **Sahar Sultan:** Supervision. **Rekha Bhat:** Supervision. **Corrado Minimo:** Supervision. **Zurab Azmaiparashvili:** Supervision, Writing – review & editing. **Sadia Benzaquen:** Supervision.

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.

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